STUDIES IN THE CHEMISTRY OF CYCLIC AND ACYCLIC NITROGEN COMPOUNDS

By

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To my husband, Abdul, for his loving support

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

STUDIES IN THE CHEMISTRY
OF CYCLIC AND ACYCLIC NITROGEN COMPOUNDS

By

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Chairman: Alan R. Katritzky, FRS
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Formic acid variously acts as a formylating, methylating, reducing and oxidizing agent in its reactions with piperidine, pyridine and some of their methyl derivatives under aquathermolysis conditions. Both pyridine and piperidine are converted in significant amounts into 1-methyl-, 1-ethyl-, 1-propyl- and 1-pentyl-piperidines. Of the 1-alkyl groups, isotopic labelling shows that only 1-methyl derives from the formic acid, while the 1-ethyl and 1-propyl arise from heterocyclic ring C-C bond fission by retro-vinylogous-bis-aza-Aldol reactions. Detailed analysis of the products for pyridine, piperidine, and their 4-methyl derivatives, reacted separately and mixed, supports mechanisms in which a piperidine adds 1,2 to a pyridinium cation, or to a di- or tetra-hydropyridine, to initiate reaction sequences leading to the product slates found.

Two primary aliphatic amines (1-octylamine, 1-dodecylamine), one secondary aliphatic amine (di-1-octylamine) and two tertiary aliphatic amines (*N*,*N*-dimethyl-1-octylamine, *N*,*N*-dimethyl-1-dodecylamine) were each heated at 250 °C and 350 °C with 49% aqueous formic acid for varying periods of time. The primary amines showed two

dominant reaction pathways viz., (i) *N*-formylation with subsequent reduction to give *N*-methyl- and *N*,*N*-dimethyl-alkylamines, and (ii) elimination of NH_3 and smaller amines to the corresponding alkenes followed by partial double bond isomerization. The secondary amine mainly underwent conventional *N*-formylation with subsequent reduction to the *N*-methyl derivative. Tertiary amines underwent reductive cleavages to secondary and primary amines, which subsequently followed the reaction sequences seen for primary amines.

Benzotriazole-1-carboxamidinium tosylate was synthesized from benzotriazole, cyanamide and *p*-toluenesulfonic acid. This tosylate salt underwent nucleophilic displacement of the benzotriazole anion by various primary and secondary amines to generate substituted guanidines under mild conditions.

Two derivatives of 4-amino-1,2,4-triazole were synthesized and their chemistries investigated. Condensation of 4-amino-1,2,4-triazole and fluorenone led to *N*-(1,2,4-triazol-4-yl)fluorenimine. This novel imine was investigated as a potential electrophilic aminating agent. 4-(Benzotriazol-1-ylmethylamino)-1,2,4-triazole was synthesized by the condensation of 4-amino-1,2,4-triazole and hydroxymethylbenzotriazole. This adduct undergoes nucleophilic displacement by Grignard reagents to generate 4-(alkylamino)-1,2,4-triazoles.

CHAPTER I
GENERAL INTRODUCTION

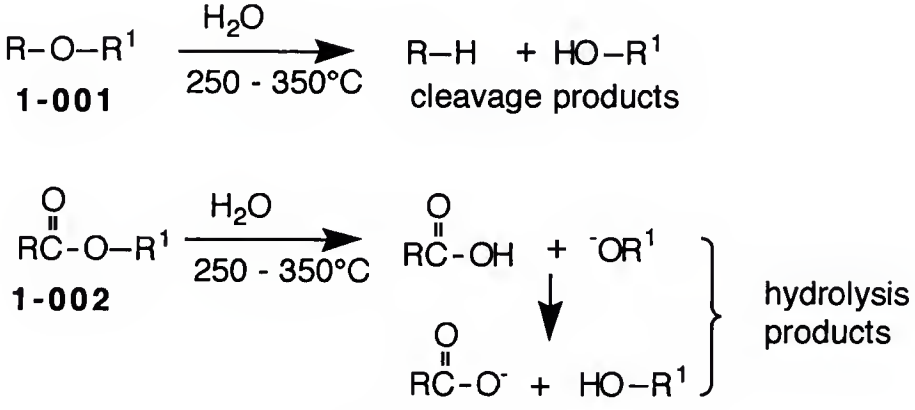
General Introduction to Nitrogen Compounds

Nitrogen is one of the principal elements in all living creatures. Therefore, nitrogen containing compounds are ubiquitous in nature. A large number of medically and biologically important compounds are N-compounds--in particular various amines and amino acids. Many of these compounds have powerful physical and psychological effects. Nitrogen compounds are also important industrially. The petrochemical industry provides raw materials for liquid petroleum and natural gas feed stocks in the form of amines, nitro-compounds, heterocyclic N-compounds, dyes, drugs etc. Due to the importance of nitrogen to the growth of plants and animals, it is not surprising that nitrogen compounds (particularly fertilizers) rank very high in total annual commercial production. The objective of this dissertation is to investigate the chemistry of cyclic and acyclic nitrogen compounds, for which the results will be reported in the following four chapters.

Introduction

Chapters II and III deal with the aquathermolysis of various classes of nitrogen compounds. Chapter II focuses upon the aquathermolysis of piperidine, pyridine and some of their methyl derivatives, while chapter III deals with the aquathermolysis of primary, secondary and tertiary aliphatic amines. Aquathermolysis, the thermal transformations of organic compounds in aqueous environments [90EF493, 91SCI231],

can be used to remove the deleterious nitrogen compounds found in crude petroleum and synthetic oils. Normally, organic compounds do not react with water under standard reaction conditions. However, organic molecules which are unreactive in liquid water can be subjected to many chemical reactions when the temperature of water is raised to 250 °C - 350 °C. Compounds such as ethers (**1-001**) and esters (**1-002**) undergo cleavage and hydrolysis, respectively, with ease [90EF488] (Scheme 1-1). An analogous process (to the above reactions): catagenesis, takes place in nature. Catagenesis, is the process by which cross-linked macromolecular structures (solid petroleum kerogens) are converted in source rock into liquid petroleum. In nature, catagenesis has a time frame of millions of years, and occurs at temperatures less than 200 °C, in aqueous environments at about 61MPa of pressure [91SCI231].



Scheme 1-1

When water is heated at elevated temperatures significant changes in its physical and chemical properties take place. As the temperature of water is increased from 25 to 350 °C the following changes take place:

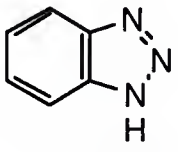
(i) the density of water decrease from 0.997 to 0.713 g/cm^3 [81MIE57]

(ii) the dielectric constant decreases from 78.85 to 19.66 [50JA2844]

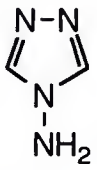
(iii) the solubility parameter decreases from 23.4 to 14.5 (cal/cm^3)$^{1/2}$ [69MI]

The physical changes allow water at 300 °C to behave similar to acetone at 25 °C [91SCI231], creating an environment for ionic reactions.

Chapter IV discusses the synthesis of benzotriazole-1-carboxamidinium tosylate and the related application of benzotriazole methodology in the synthesis of guanidines from amines. A useful synthetic auxiliary, benzotriazole (**1-003**) and its chemistry has been exploited within the Katritzky research laboratories and has also found favorable use industrially. The N-N double bond of benzotriazole has strong electron-withdrawing ability which enhances the acidic properties and therefore transforms the benzotriazole anion into an excellent leaving group. A wide variety of organic compounds including primary, secondary and tertiary amines, hydroxylamines, hydrazines, amides, polyfunctional amino compounds, ethers and esters have been synthesized [91T2683].



1-003



1-004

The structurally related 4-amino-1,2,4-triazole (**1-004**) has also been investigated. This amino-triazole can be condensed with ketones to generate the corresponding imine. In addition, this triazole can also be condensed with benzotriazole and formaldehyde to generate the corresponding benzotriazole-triazole adduct. Chapter VI deals with the derivatization of 4-amino-1,2,4-triazole and its application in the attempted synthesis of imines and 4-(alkylamino)-1,2,4-triazoles.

CHAPTER II
FIRST DEMONSTRATION OF SPECIFIC C-C BOND SCISSION OF THE PYRIDINE RING: REACTIONS OF PIPERIDINE, PYRIDINE AND SOME OF THEIR METHYL DERIVATIVES IN AQUEOUS FORMIC ACID

Introduction

Nitrogen, sulfur and oxygen are among the heteroatoms which are found in coals [92EF439]. In order to convert solid coals and oil shale kerogens to liquids which can be used as synthetic fuels (the) cross-links of the above mentioned heteroatoms need to be broken. This process of the liquification of coal normally requires a variety of catalysts [89EF160]. Unfortunately, a specific catalyst is required for the removal of a specific heteroatom and can become quite costly.

Liquids derived from N-containing coals often contain large amounts of N-impurities [84MI]. Compounds which contain nitrogen are detrimental for the following three reasons:-

(i) they poison and deactivate catalyst used later in refining processes,

(ii) they form toxic nitrogen oxides upon combustion, and

(iii) they confer instability on the product fuel, causing discoloration and other detrimental reactions [92EF439, 93TL4739].

The nitrogen-containing compounds found in petroleum or synthetic oils include both heterocycles, for example pyridines and pyrroles, and non-heterocycles such as aliphatic amines. With N-heterocycles, the normal mode of removal has been denitrogenation [93TL4739] or hydrodenitrogenation [92EF439]. Hydrodenitrogenation involves the

hydrogenolysis of strong aromatic C-N bonds which subsequently requires significant prehydrogenation of the heteroaromatic and/or aromtic rings [92EF439].

Extensive investigations have been carried out within the Katritzky Research Group on nitrogen removal from heterocyclic nitrogen model compounds in aqueous systems [92EF439, 92EF450]. Formally, we have been investigating the aquathermolysis[2.1] - i.e. thermal transformations of organic compounds in aqueous environments - of a variety of N-compounds. Recently, we found that at 350 °C, 49% aqueous formic acid induces the hydrogenation of the pyridine ring to piperidine in significant amounts and also induces the scission of the pyridine ring [93TL4739]. Over the last 50 years, much evidence has accumulated that the common heterocycles can undergo (often reversibly) ring opening under a variety of conditions. However, all examples involve the scission of heteroatom-carbon bonds; the analogy has been made of heterocycles as carbon chains with heteroatoms as padlocks which enable opening by a suitable key.

We set out to propose appropriate mechanistic pathways for the various products of pyridine ring scission, by synthesizing authentic compounds and investigating their authentic mass spectral fragmentation pathways to confirm the products of the aquathermolysis runs.[2.2,2.3] Therefore, we studied the effect of 49% aqueous formic acid on piperidine (**2-004**)[2.4], 1-methylpiperidine (**2-007**), 4-methylpiperidine (**2-008**), pyridine (**2-005**) and 4-methylpyridine (**2-012**) (Scheme 2-1). The work to be described had its origin in our extensive studies [92EF439, 92EF450] of hydrodenitrogenation of

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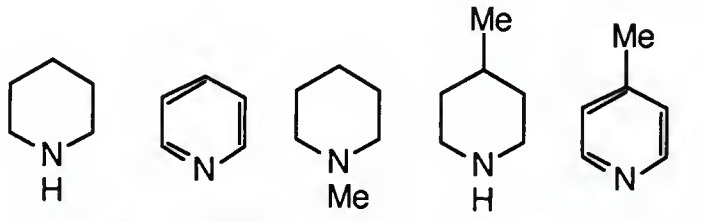
2.1 This project formed part of a joint collaboration between the Katritzky Research Group at the University of Florida and groups at Exxon Research and Engineering Co.

2.2 All aquthermolysis reactions were conducted jointly by Marudai Balasubramanian, Richard A. Barcock and Elena S. Ignatchenko at the University of Florida.

2.3 All synthesis of compounds and subsequent mass spectral investigations involved in the elucidation of product identification were performed by Roslyn L. White at the Universtiy of Florida.

2.4 Compounds have been numbered sequentially according to their retention times, with compound **2-001** bearing the lowest retention time (See Table 2-1 for a complete listing). Compound numbers equal to or greater than **2-100** are used for postulated intermediates not detected by the GC/MS analyses.

heteroaromatic models of compounds found in fuel resource streams. In addition to reporting the unique behavior of these compounds under aquathermolysis conditions, we now disclose the first examples of specific C-C-bond scission in the unactivated heterocyclic system of pyridine, and demonstrate how the long-studied industrially important processes by which pyridine rings are formed from C_1, C_2 and C_3 aldehydes are in principle reversible.



2-004 **2-005** **2-007** **2-008** **2-012**

Scheme 2-1

The gas chromatographic (GC) behavior (retention times) of all the compounds employed in this study (starting materials and products) are summarized in Table 2-1.[2.5] Tables 2-2, 2-3, and 2-4 contain the compiled mass spectral data for the analysis of the results. Table 2-2 contains the sources and purities of the starting materials used and have been compiled based upon the direct comparison of the GC retention times, and of the mass spectral (MS) fragmentation patterns with those of the authentic compounds. Table 2-3 contains compounds which have been compared with literature mass spectral data for the same compound. Those compounds for which no suitable literature MS data were available have been identified by MS fragmentation patterns (obtained from the aquathermolysis runs) and have been compiled in Table 2-4. Further explanation of the Tables 2-2--2-4 is given in section 2.6 Experimental. All the results from the aquathermolyses are collected in Tables 2-5 and 2-6. The product yields are represented as

2.5 The data has been compiled as explained in this paragraph according to the series of aquathermolysis papers [90EF499].

Table 2-1. Structure and Identification of Starting Materials and Products.

No.	t_R (min)	Structure	MW	Eq. Wt	Basis a	Factor b
2-001	0.38	pentene	70	70	Table 2-2	0.97
2-002	0.40	3-methyl-1-pentene	84	84	Table 2-2	0.97
2-003	0.43	pentylamine	87	87	Table 2-2	0.72
2-004	0.45	piperidine	85	85	Table 2-2	0.72
2-005	0.47	pyridine	79	79	Table 2-2	0.84
2-006	0.53	1-(^{13}C)-methylpiperidine	100	100	Table 2-4	0.72
2-007	0.53	1-methylpiperidine	99	99	Table 2-2	0.72
2-008	0.67	4-methylpiperidine	99	99	Table 2-2	0.72
2-009	0.68	*N*,*N*-dimethylpentylamine	115	115	Table 2-4	0.38
2-010	0.72	1,4-dimethylpiperidine	113	113	Table 2-2	0.71
2-011	0.79	1-ethylpiperidine	113	113	Table 2-2	0.71
2-012	0.82	4-methylpyridine	93	93	Table 2-2	0.83
2-013	0.91	*N*,*N*-dimethyl-2-methylpentylamine	129	129	Table 2-4	0.71
2-014	1.05	1-ethyl-4-methylpiperidine	127	127	Table 2-4	0.71
2-015	1.22	1-propylpiperidine	127	127	Table 2-4	0.71
2-016	1.60	1-propyl-4-methylpiperidine	141	141	Table 2-4	0.70
2-017	1.68	1-butylpiperidine	141	141	Table 2-3	0.70
2-018	1.95	1-butyl-4-methylpiperidine	155	155	Table 2-4	0.70
2-019	2.60	1-(2-methylbutyl)piperidine	155	77.5	Table 2-4	0.70
2-020	2.84	1-pentylpiperidine	155	77.5	Table 2-3	0.70
2-021	2.95	1-(pent-4-en-yl)piperidine	153	76.5	Table 2-4	0.70
2-022	3.10	1-(^{13}C)-formylpiperidine	114	114	Table 2-4	0.38
2-023	3.10	1-formylpiperidine	113	113	Table 2-2	0.38
2-024	3.17	1-(3-methylpentyl)piperidine	169	84.5	Table 2-4	0.69
2-025	3.21	1-pentyl-4-methylpiperidine	169	84.5	Table 2-4	0.69
2-026	3.61	1-acetylpiperidine	127	127	Table 2-2	0.54

Table 2--1 continued

No.	t_R (min)	Structure	MW	Eq. Wt	Basis a	Factor b
2-027	3.70	1-formyl-4-methylpiperidine	127	127	Table 2-4	0.38
2-028	3.76	1-(3-methylpentyl)-4 -methylpiperidine	183	91.5	Table 2-4	0.69
2-029	4.43	1-(5-aminopentyl)piperidine	170	85	Table 2-4	0.45
2-030	4.59	1-acetyl-4-methylpiperidine	141	141	Table 2-4	0.54
2-031	5.94	1-(3-methyl-5-aminopentyl)-4 -methylpiperidine	198	99	Table 2-4	0.44

t_R (min) = Retention time in minutes. MW = molecular weight. Eq. Wt = equivalent weight. a = Identification Basis, see appropriate tables. b = Response Factor, see ref [89TCM17].

Table 2-2. Authentic Compounds Used as Starting Materials and for the Identification of Products.

No.	Compound	MW	a	Purity (%)	*m/z* (% relative intensity)	Ref. b spectra#
2-001	pentene	70	A	100	70(35); 55(60); 42(100); 41(45); 39(35)	331
2-002	3-methyl-1-pentene	84	A	100	84(30); 69(80); 55(100); 41(80)	741
2-003	pentylamine	87	A	99	87(5); 70(3); 55(2); 42(3); 30(100)	921
2-004	piperidine	85	A	99	85(55); 84(100); 70(10); 56(40); 55(45)	68011
2-005	pyridine	79	A	99	79(60); 55(20); 52(100); 50(60); 44(70)	67826
2-007	1-methylpiperidine	99	A	100	99(35); 98(100); 84(10); 70(30); 58(10)	68696
2-008	4-methylpiperidine	99	A	99	99(60); 98(95); 84(40); 70(10); 56(100)	68691
2-009	*N,N*-dimethyl pentylamine	115	S	100	115(6); 58(100); 44(4); 42(10)	[c]
2-010	1,4-dimethylpiperidine	113	A	100	113(10); 112(100); 98(5); 70(20)	80481
2-011	1-ethylpiperidine	113	A	99	113(25); 112(20); 98(100); 84(10)	3071
2-012	4-methylpyridne	93	A	100	93(100); 66(50); 65(25); 51915)	68420
2-013	*N,N*-dimethyl-2-methylpentylamine	129	S	100	129(5); 100(5); 86(10); 58(100)	[c]
2-019	1-(2-methylbutyl)-piperidine	155	S	100	155(7); 98(100); 84(10); 70(6); 56(10)	[d]
2-023	1-formylpiperidine	113	A	99	113(100); 112(50); 103(30); 98(50)	3043
2-024	1-(3-methylpentyl)-piperidine	169	S	100	169(3); 154(9); 98(100); 84(5); 70(4)	[d]
2-026	1-acetylpiperidine	127	A	100	127(100); 112(20); 84(45); 70(25); 56(30)	5077

MW = molecular weight. a A = Aldrich, S = synthesized authentic compound (see experimental section). b spectral numbers of the mass spectral data for the compounds found from a search of the Wiley / NBS Registry of Mass Spectral Data Base: F.W. McLafferty, D.B. Stauffer, 1989. This book is the combination of the revisions of the following two books and their database versions: Registry of Mass Spectra data by E. Stenhagen, S. Abrahamsson and F.W. McLafferty and EPA / NIH Database by S.R. Heller, G.W. Milne and its two supplements. c no literature MS data available. d novel compound.

Table 2-3. Identification of Piperidines by Comparison of Mass Spectral Fragmentation with Literature data.

No.	Piperidine Substituent	MW	Fragmentation Found *m/z* (% rel. intensity)	Ref. a spectra #	Fragmentation Reported b *m/z* (% rel. intensity)
2-017	1-butyl-	141	141(5); 98(100); 55(5); 42(5)	8059	141(5); 98(100); 55(5); 42(5)
2-020	1-pentyl-	155	155(5); 154(10); 99(5); 98(100)	11568	155(10); 154(5); 99(5); 98(100)

MW = molecular weight. a spectral numbers of the mass spectral data for the compounds found from a search of the Wiley / NBS Registry of Mass Spectral Data Base: F.W. McLafferty, D.B. Stauffer, 1989. This book is the combination of the revisions of the following two books and their database versions: Registry of Mass Spectra data by E. Stenhagen, S. Abrahamsson and F.W. McLafferty and EPA / NIH Database by S.R. Heller, G.W. Milne and its two supplements. b Mass spectral data obtained from authentic compound (see experimental section).

Table 2-4. Identification of Piperidines from Mass Spectral Fragmentation Patterns

No.	Piperidine Substituent	MW	Fragmentation Pattern *m/z* (% rel. intensity, structure of fragment ion)
2-006	1-(^{13}C)-methyl-	100	100(75, M^+); 99(100, M-H); 71(25, M-Et); 70(10); 58(10, C_3H_8N); 43(30, C_2H_5N)
2-014	1-ethyl-4-methyl-	127	127(20, M^+); 112(100, M-CH_3); 84(20, $C_5H_{10}N^+$); 80(15); 70(40); 52(25); 42(60); 33(99)
2-015	1-propyl-	127	127(5, M^+); 126(20, M-H); 98(100, M-Et); 57(5, C_3H_7N)
2-016	1-propyl-4-methyl-	141	141(5, M^+); 112(100, M-Et); 70(25); 55(10); 44(30); 42(30)
2-018	1-butyl-4-methyl-	155	155(10, M^+); 112(100, M-Pr); 98(10); 70(35); 55(20); 44(60); 33(95)
2-021	1-(pent-4-en-1-yl)-	153	153(1, M^+); 98(100, M-C_4H_7); 84(4); 70(12)
2-022	1-(^{13}C)-formyl-	114	114(100, M^+);113(35, M-H); 98(30, M-CH_4); 84(20, M-^{13}CHO); 70(15, M-C_3H_6)
2-025	1-pentyl-4-methyl-	169	169(5, M^+); 112(100, M-C_4H_9); 84(5); 70(30); 55(5); 44(30)
2-027	1-formyl-4-methyl-	127	128(100, $M^+ + 1$); 127(10, M^+); 126(5); 112(25, M-CH_3); 98(10, M-CHO); 84(10, $C_5H_{10}N^+$)
2-028	1-(3-methylpentyl)-4-methyl-	183	183(5, M^+); 112(100, M-C_5H_{11}); 70(25, M-$C_7H_{15}N$); 55(5); 44(20); 42(10); 41(15)
2-029	1-(5-aminopentyl)-	170	170(40, M^+); 140(10, M-CH_2=NH_2^+); 112(5); 98(100); 84(10); 70(20); 58(15); 41(15); 42(35)
2-030	1-acetyl-4-methyl-	141	142(100, $M^+ + 1$); 141(25, M^+); 140(10, M-H); 126(35, M-CH_3); 98(35, M-$COCH_3$); 84(30)
2-031	1-(3-methyl-5-amino-pentyl)-4-methyl-	198	198(15, M^+); 197(5); 196(15); 112(100); 70(15); 55(10); 44(20); 42(15); 41(20)

MW = molecular weight.

percentages of moles of starting material as described in detail previously [90EF493] and have been corrected with regard to their response factors [89TCM17].[2.6] Table 2-7 demonstrates the percentages of the various simple *N*-alkylpiperidines formed from pyridine and their 4-methyl derivatives, singly and admixed. Structures and proposed mechanistic pathways for the formation of these products (which are justified later in this chapter) are given in Schemes 2-3, 2-8--2-12. In these reaction Schemes, numbers greater than **2-100** are used for postulated intermediates not detected by the GC/MS analyses.

Synthesis of Compounds

In the project outlined above, undertaken in our laboratories, on the aquathermolysis of piperidine, pyridine and some of their methyl derivatives in 49% aqueous formic acid solutions, we were speculating upon the formation of some 1-alkylpiperidines and tertiary aliphatic amine derivatives as the aquathermolysis reactions progressed. However, the gas chromatographic/mass spectral data was inconclusive for the compounds were hitherto unknown. Thus, we were interested in synthesizing these various 1-alkylpiperidines and *N,N*-dimethylalkylamines and determining their authentic mass spectral fragmentation pathways, to confirm the identity of these products in the aquathermolyses, as well as giving us an idea about the identity of similar derivatives.

The compounds synthesized were authentic samples of two tertiary amines, *N,N*-dimethylpentylamine (**2-009**) and *N,N*-dimethyl-2-methylpentylamine (**2-013**), and three 1-alkylpiperidines, 1-(2-methylbutyl)piperidine (**2-019**), 1-(3-methylpentyl)piperidine (**2-024**) and 1-(4-methylpentyl)piperidine (**2-032**) (Scheme 2-2). The novel cyclic amines (**2-019**, **2-024**) and the known cyclic amine (**2-032**) were prepared in respectable yields by the reactions of 1-(piperidinomethyl)benzotriazole (**2-033**) with the Grignard reagents

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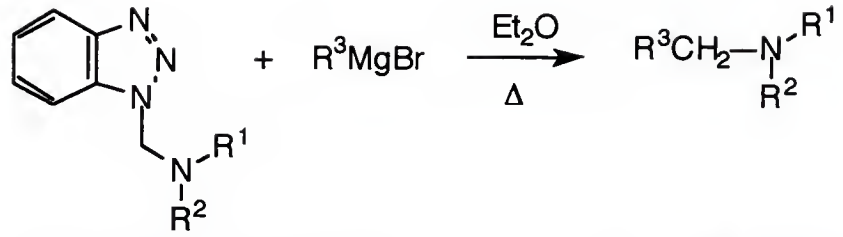
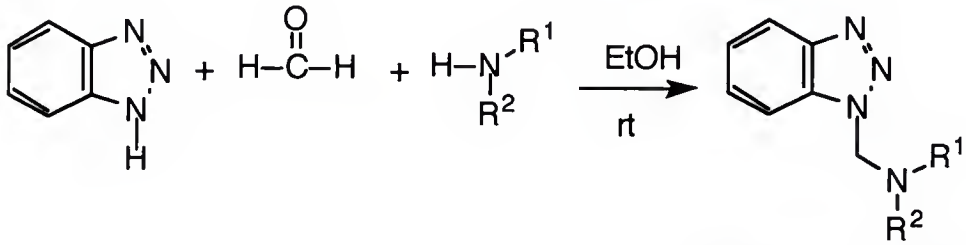
2.6 The possibility of calculating the response factor allows for the quantitative analysis of complex product mixtures by GC/MS - especially for those cases where some or all of the products are unavailable.



2-033 R^1 , R^2 = -$(CH_2)_5$-
2-034 $R^1 = R^2$ = Me

2-009, **2-013**,
2-019, **2-024**, **2-032**

Compound	R^1	R^2	R^3	(%) yield
2-033	-$(CH_2)_5$-		___	94
2-034	Me	Me	___	83
2-009	Me	Me	$CH_2CH_2CH_2CH_2$	27
2-013	Me	Me	$CH_3CH_2CH_2(CH_3)CH$	28
2-019	-$(CH_2)_5$-		$CH_3CH_2(CH_3)CH$	62
2-024	-$(CH_2)_5$-		$CH_3CH_2CH(CH_3)CH_2$	76
2-032	-$(CH_2)_5$-		$(CH_3)_2CHCH_2CH_2$	57



2-033 R^1 , R^2 = -$(CH_2)_5$-
2-034 $R^1 = R^2$ = Me

Scheme 2-2

of 2-bromobutane, 1-bromo-2-methylbutane and 1-bromo-3-methylbutane, respectively. The tertiary, acyclic amines (**2-009**, **2-013**) were prepared by the reaction of 1-(*N*,*N*-dimethylaminomethyl) benzotriazole (**2-034**) with the corresponding Grignard reagents of *n*-butyl bromide and 2-bromopentane, respectively (see section 2.6 Experimental).

1-(Piperidinomethyl)benzotriazole (**2-033**) [52JA3868, 87JCS(P1)799] and 1-(*N*,*N*-dimethylaminomethyl)benzotriazole (**2-034**) [46JA2496, 92JOC4932] were prepared in high yields employing literature procedures. The benzotriazole adduct **2-033** was synthesized by condensation of benzotriazole formaldehyde and piperidine, while adduct **2-034** was synthesized by the condensation of benzotriazole, formaldehyde and dimethylamine (Scheme 2.2). Further discussion of the mass spectral identification and interpretation of the amines is covered in the Discussion (2.4), Experimental (2.6) and Appendix.

Results

Piperidine (**2-004**). On heating with aqueous 49% HCO_2H at 350 °C for 2 h, piperidine (**2-004**) was completely consumed (Table 2-5). The major product was 1-formylpiperidine (**2-023**, 93.9%) together with an appreciable amount of 1-methylpiperidine (**2-007**, 4.1%). However, 1-ethyl- (**2-011**, 0.3%), 1-propyl- (**2-015**, 0.8%) and 1-acetyl-piperidine (**2-026**, 0.8%) were all detected as minor products along with traces of 1-pentylpiperidine (**2-020**, 0.1%). After 8 h at 350 °C in 49% HCO_2H, the yield of 1-formylpiperidine (**2-023**) was roughly halved (42.4%) and the aforementioned 1-alkylpiperidines, noticeably 1-pentylpiperidine (**2-020**, 19.3%) were all formed in larger amounts. 1-(2-Methylbutyl)piperidine (**2-019**) was formed in trace amount (0.6%). It is clear that 1-formylpiperidine (**2-023**) initially formed is later converted into 1-methylpiperidine (**2-007**), and *via* deformylation into the other 1-alkylpiperidines.

Table 2-5. Products Obtained from 1-Methylpiperidine (1-MePip), 4-Methylpiperidine (4-MePip), Piperidine (Pip).

Additive		Mech Type	1-MePip				4-MePip				Pip		
			-	-	-	-	-	x	y	-	-	-	z
Time (h)		(see text)	0.5	2	4	8	2	2	2	8	2	8	2
No.	Structure												
2-001	pentene	-	-	-	-	-	-	-	-	-	-	1.6	-
2-003	pentylamine	(iii)	-	-	-	-	-	-	-	-	-	2.0	-
2-004	piperidine	-	1.8	4.1	5.8	-	-	-	0.4	-	-	-	-
2-005	pyridine	-	-	-	-	-	-	(25.6)+	-	-	-	-	-
2-007	1-methylpiperidine	(i)	53.8	47.9	51.7	23.4	-	3.6	-	-	4.1	23.2	3.9
2-009	*N,N*-dimethylpentylamine	(iii)	-	-	2.2	23.1	-	-	-	-	-	-	-
2-010	1,4-dimethylpiperidine	(i)	-	-	-	-	27.5	2.7	13.7	38.0	-	-	-
2-011	1-ethylpiperidine	(ii)	1.5	4.8	9.0	23.3	-	0.5	-	-	0.3	0.9	0.6
2-013	*N,N*-dimethyl-2-methyl-pentylamine	(iii)	-	-	0.4	-	-	-	-	-	-	-	-
2-014	1-ethyl-4-methylpiperidine	(ii)	-	-	-	-	0.1	1.1	0.4	6.9	-	-	-
2-015	1-propylpiperidine	(ii)	0.9	2.1	2.4	14.9	-	0.7	-	-	0.8	2.4	0.5
2-016	1-propyl-4-methylpiperidine	(ii)	-	-	-	-	-	1.9	0.1	9.3	-	-	-
2-017	1-butylpiperidine	(ii)	1.6	0.6	1.1	1.3	-	-	-	-	-	-	-
2-018	1-butyl-4-methylpiperidine	(ii)	-	-	-	-	-	-	-	0.5	-	-	-
2-019	1-(2-methylbutyl)piperidine	(ii)	-	-	-	-	-	0.3	-	-	-	0.6	-
2-020	1-pentylpiperidine	(iv)	3.7	6.5	5.5	4.8	-	0.3	-	-	0.1	19.3	0.1
2-021	1-(pent-4-en-1-yl)piperidine	(iv)	6.3	1.2	0.5	0.7	-	-	-	-	-	-	-
2-023	1-formylpiperidine	(i)	29.0	28.3	15.1	2.4	-	11.9	-	-	93.9	42.4	94.9
2-025	1-pentyl-4-methylpiperidine	(ii)	-	-	-	-	-	2.3	-	0.6	-	-	-
2-026	1-acetylpiperidine	(i)	1.4	4.5	6.3	6.1	-	-	-	-	0.8	1.0	-
2-027	1-formyl-4-methylpiperidine	(i)	-	-	-	-	70.1	46.5	83.1	33.3	-	-	-
2-028	1-(3-methylpentyl)-4-methyl piperidine	(ii)	-	-	-	-	-	0.5	-	7.0	-	-	-
2-029	1-(5-aminopentyl)piperidine	(iii)	-	-	-	-	-	0.6	-	-	-	-	0.1
2-030	1-acetyl-4-methylpiperidine	(ii)	-	-	-	-	-	1.3	3.3	-	-	-	-
2-031	1-(3-methyl-5-aminopentyl)-piperidine	(ii)	-	-	-	-	2.3	1.5	1.0	1.1	-	-	-

x = pyridine; y = 3-methyl-1-pentene; z = pentene; + = residual pyridine from additive

Piperidine (**2-004**) plus 1-pentene (**2-001**). The same reaction of piperidine was carried out in the presence of 1-pentene (**2-001**) (1 equivalent) in 49% HCO_2H at 350 °C for 2 h and gave the same slate of products as in the absence of pentene, i.e. 1-methyl-(**2-007**, 3.9%) and 1-formyl-piperidine (**2-023**, 94.9%), together with the same minor products. In particular, no significant increase in 1-pentylpiperidine (**2-020**) was found in this run, suggesting that olefins are not intermediates in these reactions.

1-Methylpiperidine (**2-007**). This compound showed a 46.2% conversion after just 0.5 h at 350 °C in 49% HCO_2H. The major product was 1-formylpiperidine (**2-023**, 29.0%). This product is probably formed *via* the *N*-formylation of 1-methylpiperidine with the subsequent elimination of a methyl cation probably assisted by the formate ion. Other products included piperidine (**2-004**, 1.8%), and small quantities of 1-ethyl- (**2-011**, 1.5%), 1-propyl- (**2-015**, 0.9%), 1-butyl- (**2-017**, 1.6%) and 1-pentylpiperidine (**2-020**, 3.7%). Extending the reaction time to 2 h yielded a similar product slate, although a higher conversion (52.1%) was observed. The major product was again 1-formylpiperidine (**2-023**, 28.3%). The *N*-alkylpiperidines observed in the above reaction (350 °C, 0.5 h) were again seen here, but in increased amounts (see Table 2-5). Extending the reaction time further to 4 h, led to a 48.3% conversion, which is only slightly lower than that observed for the 2 h run. The major product here is again 1-formylpiperidine (**2-023**, 15.1%). *N,N*-Dimethyl-2-methylpentylamine (**2-013**) was formed in trace amount (0.3%), while *N,N*-dimethylpentylamine (**2-009**) was observed slightly higher (2.2%). However, it seems likely that during the extended time of this reaction, some of the 1-formylpiperidine is reduced by hydride ion from the formic acid to return to 1-methylpiperidine (**2-007**) in view of the increased amounts of the same higher *N*-alkylpiperidines which were observed (see Table 2-5). On heating at 350 °C for 8 h with 49% HCO_2H, 1-methylpiperidine (**2-007**) underwent a 76.6% conversion (Table 2-5). Again, there was a significant increase in the formation of *N*-alkylpiperidines which included 1-ethyl- (**2-011**, 23.3%), 1-propyl- (**2-015**, 14.9%), 1-butyl- (**2-017**, 1.3%),

and 1-pentyl-piperidine (**2-020**, 4.8%). *N*,*N*-Dimethylpentylamine (**2-009**) was formed in 23.1%. After 8 h, 1-formylpiperidine (**2-023**) was present only in a small amount (2.4%).

4-Methylpiperidine (**2-008**). This compound underwent complete conversion after 2 h (see Table 2-5) and the major products were 1,4-dimethylpiperidine (**2-010**, 27.5%), 1-formyl-4-methylpiperidine (**2-027**, 70.1%) and 1-(3-methyl-5-aminopentyl)-4-methylpiperidine (**2-031**, 2.3%). A trace amount of 1-ethyl-4-methylpiperidine (**2-014**, 0.1%) was also seen. At 350 °C for 8 h in 49% HCO_2H, 4-methylpiperidine (**2-008**) underwent a complete conversion to give 1,4-dimethylpiperidine (**2-010**, 38.0%), 1-formyl-4-methylpiperidine (**2-027**, 33.3%), together with smaller amounts of 1-ethyl- (**2-014**, 6.9%), 1-propyl- (**2-016**, 9.3%), 1-butyl- (**2-018**, 0.5%) and 1-pentyl- (**2-025**, 0.6%) and 1-(3-methylpentyl)-4-methylpiperidines (**2-028**, 7.0%). It will be demonstrated that the *N*-alkyl groups on the nitrogen-functionality are now derived from the 4-methylpiperidine (**2-008**) ring.

4-Methylpiperidine (**2-008**) plus 3-methyl-1-pentene (**2-002**). This run was carried out to determine whether or not 3-methyl-1-pentene (**2-002**) is an intermediate in the formation of **2-028** from **2-008**. 4-Methylpiperidine (**2-008**) on heating with 49% HCO_2H at 350 °C for 2 h, in the presence of one equivalent of 3-methyl-1-pentene (**2-002**), underwent a 100% conversion with the major products being 1,4-dimethylpiperidine (**2-010**, 13.7%) and 1-formyl-4-methylpiperidine (**2-027**, 83.1%). The product slate from this run (Table 2-5) suggests that 3-methyl-1-pentene (**2-002**) does not play a significant role in the generation of the products, especially as 1-(3-methylpentyl)-4-methylpiperidine (**2-028**), was not seen in increased amounts.

Pyridine (**2-005**). Pyridine (**2-005**) on heating with 49% HCO_2H 350 °C for 2 h underwent a 16% conversion into 1-methyl- (**2-007**, 0.9%), 1-ethyl- (**2-011**, 2.3%), 1-propyl- (**2-015**, 3.6%), 1-pentyl- (**2-020**, 1.2%) and 1-formyl-piperidine (**2-023**, 8%) (Table 2-6). Heating in 49% HCO_2H at 350 °C for 4 h, increased the conversion from

Table 2-6. Products Obtained from 4-Methylpyridine (4-MePy), Pyridine (Py).

Additive		Mech Type	4-MePy			Py		
Time (h)		(see text)	-	w	-	-	-	*
No.	Structure		2	2	6	2	4	2
2-004	piperidine	-	-	-	-	-	-	0.5
2-005	pyridine	-	-	-	-	84.0	40.3	68.6
2-006	1-(^{13}C)-methylpiperidine	(ii)	-	-	-	-	-	1.9
2-007	1-methylpiperidine	(i)	-	3.4	-	-	0.9	7.9
2-010	1,4-dimethylpiperidine	(i)	14.9	0.4	18.2	-	-	-
2-011	1-ethylpiperidine	(ii)	-	2.4	-	2.3	2.4	1.5
2-012	4-methylpyridine	-	40.4	41.1	35.4	-	-	-
2-014	1-ethyl-4-methylpiperidine	(ii)	1.4	0.4	2.8	-	-	-
2-015	1-propylpiperidine	(ii)	0.3	-	0.8	3.6	6.6	2.1
2-016	1-propyl-4-methylpiperidine	(ii)	-	0.2	1.8	-	-	-
2-017	1-butylpiperidine	(ii)	-	0.1	-	-	-	-
2-018	1-butyl-4-methylpiperidine	(ii)	0.5	1.6	0.1	-	-	-
2-019	1-(2-methylbutyl)piperidine	(ii)	-	-	-	-	1.8	-
2-020	1-pentylpiperidine	(iv)	-	0.8	-	1.2	11.7	6.7
2-022	1-(^{13}C)-formylpiperidine	(i)	-	-	-	-	-	19.2
2-023	1-formylpiperidine	(i)	-	33.8	-	8.0	24.6	-
2-024	1-(3-methylpentyl)piperidine	(iv)	-	0.3	-	-	-	-
2-025	1-pentyl-4-methylpiperidine	(ii)	-	-	1.3	-	-	-
2-026	1-acetylpiperidine	(i)	-	12.9	-	-	2.1	-
2-027	1-formyl-4-methylpiperidine	(i)	36.5	-	30.1	-	-	-
2-028	1-(3-methylpentyl)-4-methyl piperidine	(ii)	5.1	3.0	9.7	-	-	-
2-029	1-(5-aminopentyl)piperidine	(iii)	-	-	-	-	2.1	-
2-030	1-acetyl-4-methylpiperidine	(ii)	-	0.8	0.7	-	-	-

w = piperidine; * = 100% H^{13}CO$_2$H

16% to 59.7% and produced all the foregoing products in much increased quantities, together with 1-acetylpiperidine (**2-026**, 2.1%), 1-(2-methylbutyl)piperidine (**2-019**, 1.8%) and 1-(5-aminopentyl)-piperidine (**2-029**, 2.1%).

On heating in 100% $H^{13}CO_2H$ at 350 °C for 2 h, pyridine (**2-005**) showed a 31.5% conversion into a similar slate of products (but in increased amounts, probably facilitated by the use of 100% HCO_2H - see Table 2-6) as seen for the run in 49% HCO_2H at 350 °C for 2 h. Significantly, only the 1-methylpiperidine (**2-006**, 1.9%) and the 1-formylpiperidine (**2-022**, 19.2%) were labelled, and each contained just one ^{13}C label. The fact that 1-ethyl- (**2-011**, 1.5%), 1-propyl- (**2-015**, 2.1%), and 1-pentyl-piperidine (**2-020**, 6.7%) produced simultaneously had no ^{13}C labelled carbons shows conclusively that the ethyl, propyl and pentyl groups in **2-011**, **2-015** and **2-020**, respectively, are all derived completely from pyridine carbon atoms and not from carbons of the formic acid.

4-Methylpyridine (**2-012**). 4-Methylpyridine (**2-012**) on heating in 49% HCO_2H at 350 °C for 2 h showed a 59.6% conversion into 1,4-dimethyl- (**2-010**, 14.9%), 1-formyl-4-methyl- (**2-027**, 36.5%) and 1-(3-methylpentyl)-4-methyl-piperidine (**2-028**, 5.1%) together with smaller amounts of 1-ethyl- (**2-014**, 1.4%) and 1-butyl-4-methylpiperidine (**2-018**, 1.6%) (Table 2-6). Evidently, the ethyl and butyl groups required for the *N*-alkylation of 4-methylpiperidine were derived by fragmentation of 4-methylpyridine molecules. 1-(3-Methylpentyl)piperidine (**2-024**) was observed in trace amount (0.3%). 4-Methylpyridine (**2-012**) on heating in 49% HCO_2H at 350 °C for 6 h underwent a 64.6% conversion to 1,4-dimethylpiperidine (**2-010**, 18.2%), 1-formyl-4-methylpiperidine (**2-027**, 30.1%), and 1-(3-methylpentyl)-4-methylpiperidine (**2-028**, 9.7%). Other products included small amounts of 1-ethyl- (**2-014**), 1-propyl- (**2-016**), 1-butyl- (**2-018**), 1-pentyl- (**2-025**) and 2-acetyl- (**2-030**) -4-methylpiperidines.

4-Methylpiperidine (**2-008**) plus pyridine (**2-005**). To understand the types of intermediates involved in the C-C and C-N bond cleavages, we ran an aquathermolysis of 4-methylpiperidine (**2-008**) mixed with pyridine (**2-005**) (1 mole equivalent) in 49% HCO_2H at 350 °C for 2 h (Table 2-5). 4-Methylpiperidine (**2-008**) underwent a 100% and pyridine a 74.6% conversion under these conditions. Various *N*-substituted piperidines (**2-007**, **2-011**, **2-015**, **2-019**, **2-020**, **2-023** and **2-029**) were formed together with the following *N*-substituted-4-methylpiperidines; 1,4-dimethyl- (**2-010**, 2.7%), 1-ethyl-4-methyl- (**2-014**, 1.1%), 1-propyl-4-methyl- (**2-016**, 1.9%), 1-pentyl-4-methyl- (**2-025**, 2.3%), 1-(3-methylpentyl)-4-methyl- (**2-028**, 0.5%), 1-(3-methyl-5-aminopentyl)-4-methyl- (**2-031**, 2.3%) and 1-formyl-4-methylpiperidine (**2-027**, 46.5%).

4-Methylpyridine (**2-012**) plus piperidine (**2-004**). This reaction was carried out in order to compare the results with those obtained from the 4-methylpiperidine (**2-008**) plus pyridine (**2-005**) run. 4-Methylpyridine (**2-012**) showed a 58.9% conversion with 49% HCO_2H at 350 °C for 2 h and the same slate of products was seen as in the case of 4-methylpiperidine (**2-008**) plus pyridine (**2-005**) (Table 2-6). The long list of products can be classified into two groups: (i) *N*-substituted piperidines (**2-007**, **2-011**, **2-015**, **2-017**, **2-020**, **2-023**, **2-024** and **2-026**) and (ii) 4-methyl-*N*-substituted piperidines (**2-010**, **2-014**, **2-016**, **2-018**, **2-028**, and **2-030**). No piperidine (**2-004**) or 4-methylpiperidine (**2-008**) (reduction product of 4-methylpyridine {**2-012**}) was left in the reaction mixture which indicates that they were completely consumed in further reactions.

General Discussion

The most striking feature of the results is that the products comprise a relatively small number of specifically *N*-substituted piperidines. The experiment using $H^{13}CO_2H$ shows conclusively that, apart from the *N*-methyl, all the other *N*-alkyl groups are formed

from the ring carbon atoms. The fact that piperidine (**2-004**) forms a rather similar slate of products to that obtained from pyridine (**2-005**), suggest that formic acid acts not only as a reducing, but also evidently toward piperidine (**2-004**) as an oxidizing agent, although we have been unable to find literature precedence for this. We believe that most of the products formed can be explained by four types of mechanistic routes:

(i) Conventional reactions where the formic acid is behaving as a hydride ion donor and as a formylating agent.

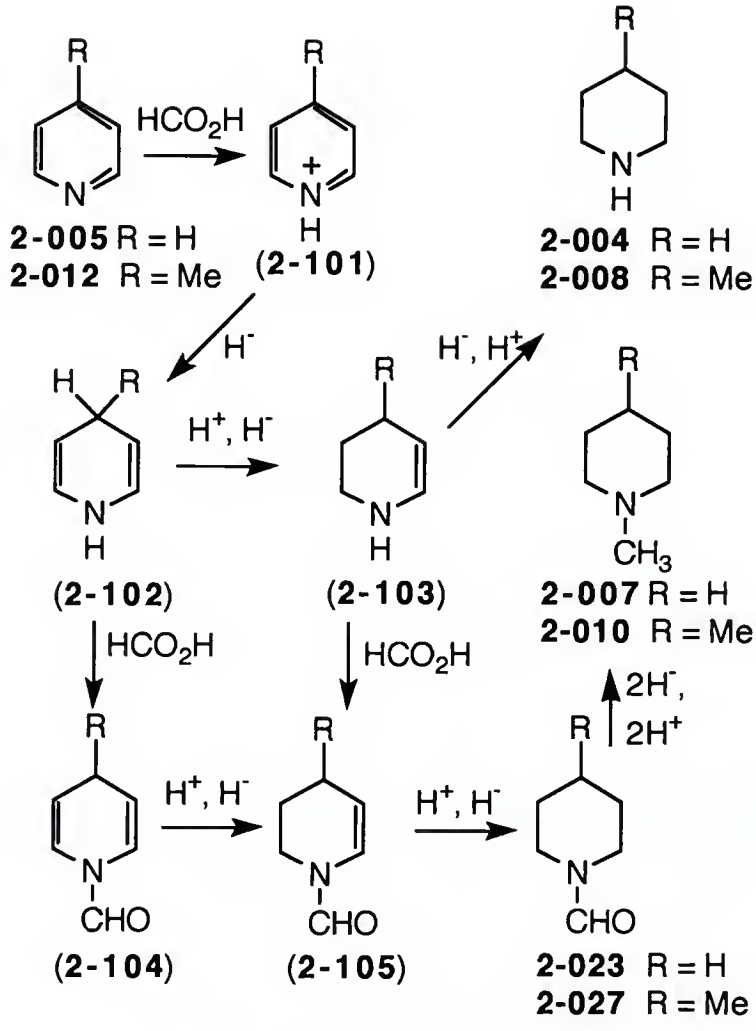
(ii) Retro-vinylogous-bis-aza-aldol reactions of products formed by the addition of piperidines to dihydropyridines.

(iii) Simple ring-opening of amidine or aminal type intermediates formed by addition of piperidine to dihydro- or tetrahydro-pyridines followed by reduction.

(iv) Ring-opening of isomers of products formed by addition of piperidines to a quaternized pyridinium cation.

We now discuss each of these mechanistic pathways in turn.

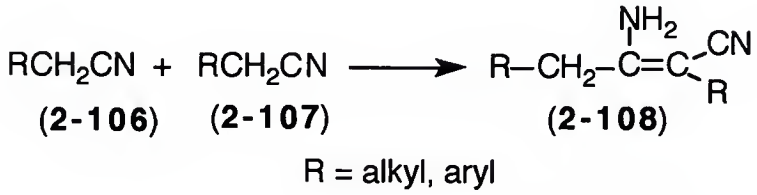
(i) Conventional formic acid reduction/formylation. Formic acid reductions of quaternary salts of pyridine and of 1-methylpyridinium cation to the corresponding fully hydrogenated products, *viz.* piperidine (**2-004**) and 1-methylpiperidine (**2-007**), are well documented [55ZOK1947, 57ZOK3021, 65CCC1700, 65Ml1058] The mechanistic pathway [38CCC66, 47CCC71] to these compounds (Scheme 2-3) involves formic acid (or formate anion) donating hydride ion to the C-4 of the pyridinium cation (**2-101**) resulting in 1,4-dihydropyridine (**2-102**). Further successive protonations and attacks of hydride ion at C-6 and C-2 yield piperidines (**2-004** and **2-008**). Piperidine (**2-004**) undergoes formylation to 1-formylpiperidine (**2-023**) which is reduced to 1-methylpiperidine (**2-007**) in the presence of formic acid as shown in Scheme 2-3. In the same manner 4-methylpiperidine (**2-008**), formed from 4-methylpyridine (**2-012**), is converted successively into 1-formyl-4-methylpiperidine (**2-027**) and 1,4-dimethylpiperidine (**2-010**).



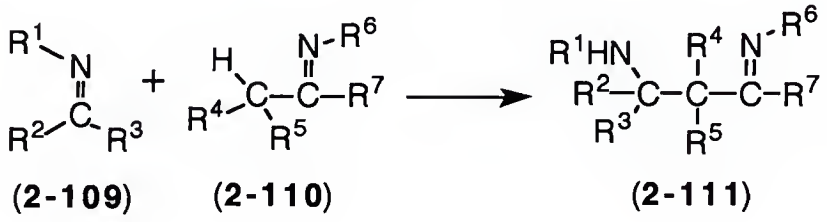
Scheme 2-3

(ii) Retro-vinylogous-bis-aza-Aldol reaction route. The Aldol reaction [68OR1] and its reverse, the retro-Aldol reaction [89MI199], are among the most important reactions in organic chemistry. Mono-aza-Aldol reactions are also well known [68AG(E)7]. Although the self-condensation of nitriles (Scheme 2-4) is a well known "named reaction" (Thorpe-reaction) [06JCS1906], we have been unable to find any example of the similar self-condensation of imines which would constitute a bis-aza-Aldol reaction, ie., a transformation of the type **2-109** plus **2-110** -> **2-111**. The retro-bis-aza-Aldol reaction,

which should thus involve the fragmentation of a β-amino-imine (**2-111**) into two imines (**2-109** and **2-110**) also appears to be unknown (Scheme 2-5).

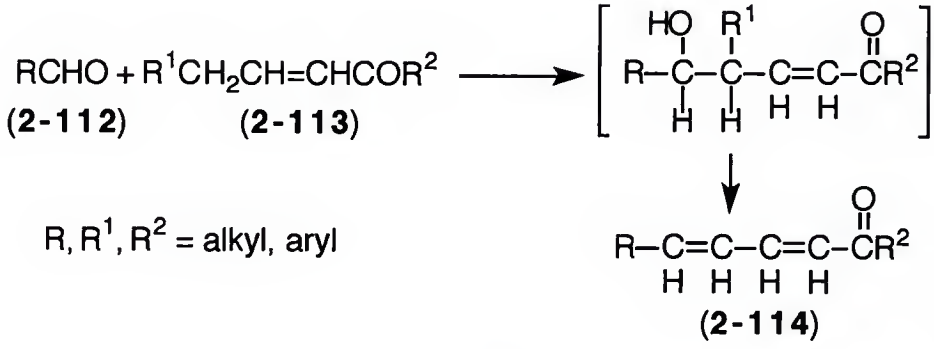


Scheme 2-4



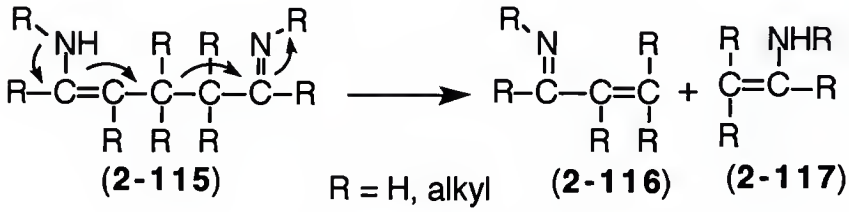
Scheme 2-5

As regards vinylogs of the Aldol reaction, although the reactions of aldehydes at the γ-position of an α,β-unsaturated ketone (Scheme 2-6) is well known [68OR1], we have been unable to find any example when this reaction stops at the intermediate hydroxy compound.



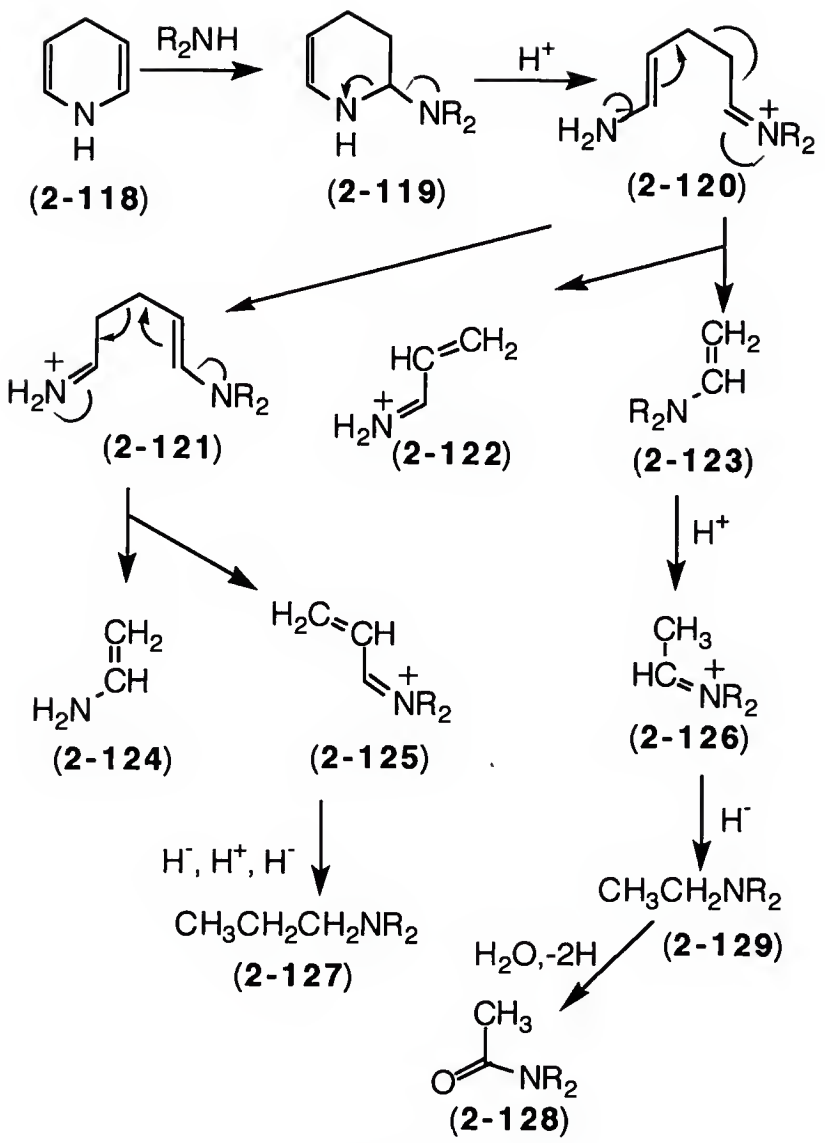
Scheme 2-6

Aza analogs of vinylogous Aldol reactions also appear to be uninvestigated although such reactions are almost certainly involved in the commercially important preparation of pyridines from aliphatic aldehydes and ammonia (see later). Based on the previous arguments, δ-amino-γδ-unsaturated imines could be expected to undergo retro-vinylogous-bis-aza-Aldol (RVBAA) reactions *cf* **2-115 -> 2-116** & **2-117** (Scheme 2-7).



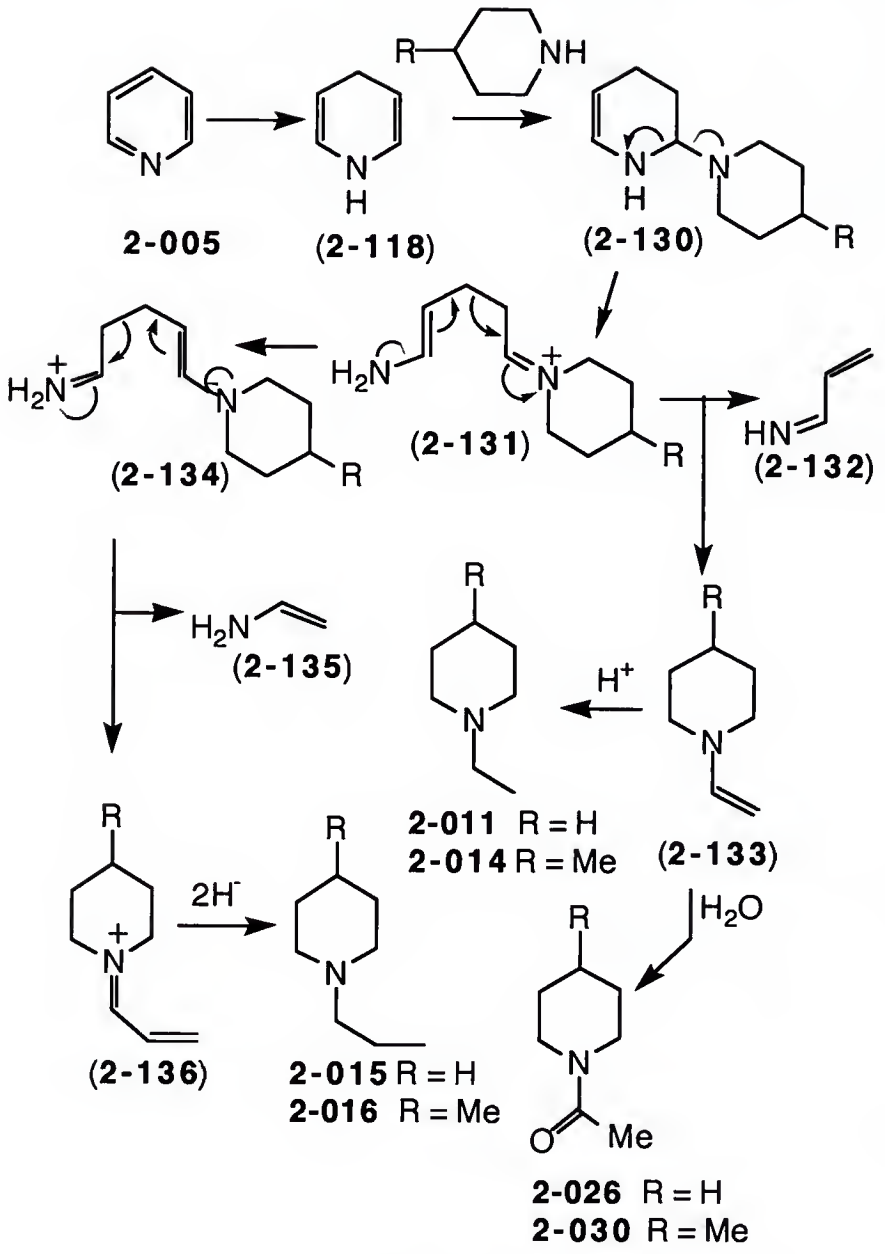
Scheme 2-7

Compounds of type **2-115** are tautomers of δ-bis-imines, and the related cations (*cf.* **2-120**) are capable of formation by ring-opening of the addition products (**2-119**) of a secondary amine (R_2NH) to a 1,4-(or 5,6-) dihydropyridine (**2-118**) (see Scheme 2-8). The RVBAA reaction of **2-120** thus causes scission into protonated acrylaldehyde imine (**2-122**) and the *N*-vinyl derivative (**2-123**) of the original secondary amine. This *N*-vinyl compound (**2-123**) is rapidly converted by successive H^+ and H^- addition (both supplied by formic acid) into the corresponding *N*-ethyl derivative (**2-129**). In addition, intermediate **2-120** can undergo proton loss and proton addition to give the isomeric δ-amino-γδ-unsaturated imine cation **2-121**. The RVBAA reaction of **2-121** affords vinylamine **2-124** and the unsaturated imine cation **2-125**, the latter which is converted rapidly, by successive additions of H^-, H^+, and H^-, into the propyl derivative **2-127** of the original secondary amine. The acetyl derivative **2-128** can also be formed from **2-126** by hydration and oxidation and this variation corresponds to the experimentally found products **2-026** and **2-030**.



Scheme 2-8

The formation of 1-ethyl- (**2-011**) and 1-propyl-piperidine (**2-015**) from the reaction of pyridine (**2-005**), (and of piperidine {**2-004**}) with formic acid are thus explained by the transformation of Scheme 2-9. Moreover, it would be expected that 4-methylpyridine (**2-012**) (and also 4-methylpiperidine {**2-008**}) would under similar conditions form 1-alkyl-4-methylpiperidines, as is observed experimentally.



Scheme 2-9

Further evidence for the mechanism proposed can be derived from the selected data of Tables 2.5 and 2-6 which have been abstracted into Table 2-7. This compares the

Table 2-7. Comparison of the Percentages of some of the *N*-Alkylpiperidines formed from Pyridine (Py) and Piperidine (Pip) and their 4-Methyl Derivatives, Singly and Admixed in 49% HCO_2H at 350 °C for 2 h.

Entry	No.	Piperidine Product Substituent	Origin of † Ring	Origin of † *N*-alkyl	4-MePy	Pip	4-MePy +Pip	4-MePip +Py	4-MePip	Py
i	**2-011**	1-ethyl-	H	Either	-	0.3	2.4	0.5	-	2.3
ii	**2-014**	1-ethyl-4-methyl-	Me	Either	1.4	-	0.4	1.1	0.1	-
iii	**2-015**	1-propyl-	H	H	-	0.8	0.3	0.7	-	3.6
iv	**2-016**	1-propyl-4-methyl-	Me	H	-	-	0.2	1.9	-	-
v	**2-017**	1-butyl-	H	Me	-	-	0.1	-	-	-
vi	**2-018**	1-butyl-4-methyl	Me	Me	1.6	-	0.1	-	-	-
vii	**2-020**	1-pentyl-	H	H	-	0.1	0.8	0.3	-	1.2
vii	**2-024**	1-(3-methyl-pentyl)-	H	Me	-	-	0.3	-	-	-
ix	**2-025**	*N*-pentyl-4-methyl-	Me	H	-	-	-	2.3	-	-
x	**2-028**	1-(3-methyl pentyl)-4-methyl-	Me	Me	5.1	-	0.3	0.5	-	-
xi	**2-011, 015, 017, 020, 024***		H	Either	0	1.2	3.9	1.5	0	7.1
xii	**2-014, 016, 018, 025, 028***		Me	Either	8.1	0	3.7	3.5	0.1	0
xiii	**2-015, 016, 020, 025***		Either	H	0	0.9	1.3	2.9	0	4.8
xiv	**2-017, 018, 024, 028***		Either	Me	6.7	0	3.5	0.5	0	0

† H is from Py or Pip; Me is from 4-MePy or 4-MePip ; * = total for compounds listed.

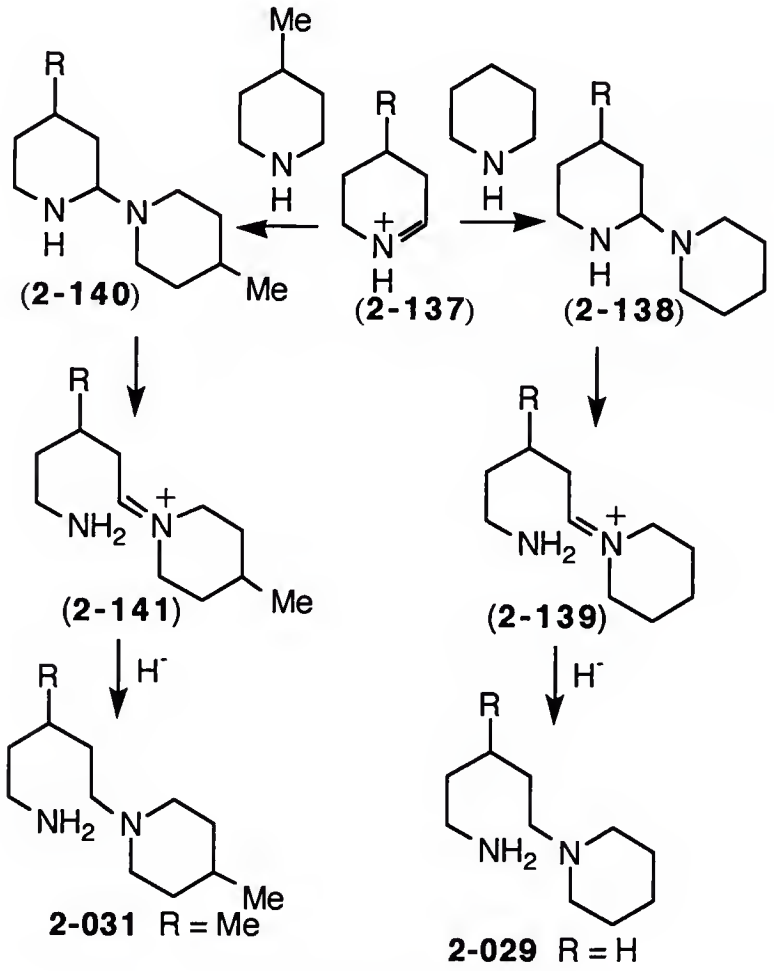
amounts of the simple *N*-alkylpiperidines formed from piperidine (**2-004**), 4-methylpiperidine (**2-008**), pyridine (**2-005**), and 4-methylpyridine (**2-012**) alone with those from the two mixed runs. Table 2-7 demonstrates very clearly that the products expected from the mechanistic routes discussed, and only the expected products, are formed in the runs from a single substrate.

Furthermore, Table 2-7 provides good evidence for the mechanism postulated from the nature, and the proportions of the products formed in the mixed runs. Thus, when 4-methylpiperidine (**2-008**) and pyridine (**2-005**) were reacted together, the 4-methylpiperidine (**2-008**) predominately provided the ring component of the piperidines formed (compare 3.5% to 1.5%; Entries xii and xi, respectively), whereas pyridine predominately provided the piperidine *N*-alkyl substituent (compare 2.9% to 0.5%; Entries xiii and xiv, respectively). Conversely, when a mixture of piperidine (**2-004**) and 4-methylpyridine (**2-012**) was reacted a total of 3.9% of products formed was derived from piperidine (**2-004**) reacting as the amine HNR_2, compared with 3.7% from the 4-methylpyridine (**2-012**) reacting as HNR_2. Again, the *N*-alkyl groups of the piperidine products were formed 1.3% from the starting piperidine and 3.5% from the 4-methylpyridine. This is in good agreement with the mechanism proposed in Scheme 2-9 in which the saturated secondary amine adds to a dihydropyridine in a key step.

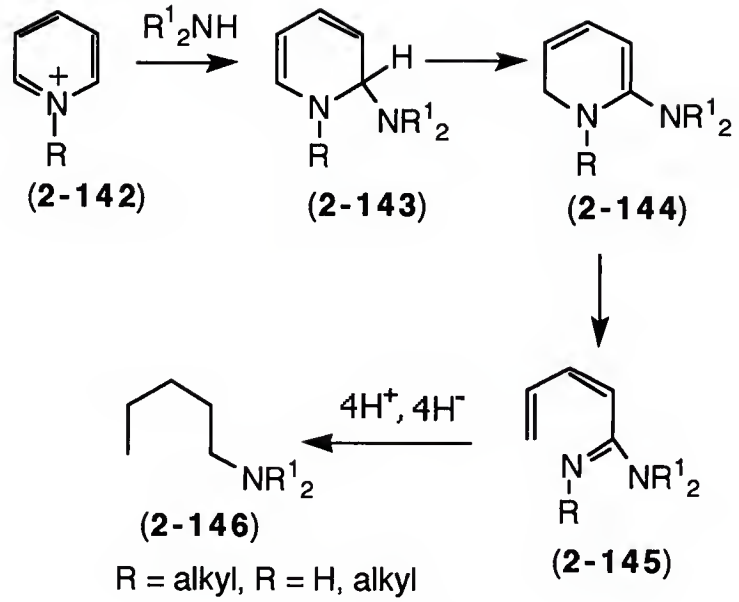
(iii) Addition to 2,3,4,5-tetrahydropyridinium cations. A simpler sequence of addition of R_2NH to a 2,3,4,5-tetrahydropyridinium ring (**2-137**) followed by ring-opening and reduction leads to amines of type $R_2N(CH_2)_5NH_2$ and this explains the formation of **2-029** and **2-031** (Scheme 2-10).

(iv) Ring opening of isomers of products of addition of piperidines to quaternized pyridines. Addition of a secondary amine to a quaternized pyridine (**2-142**) will give addition product **2-143** (see Scheme 2-11). We postulate that a 1,5-hydrogen shift in **2-143** leads to **2-144** which can undergo electrocyclic ring-opening to **2-145**. Next, four successive protonations, each followed by a hydride ion addition,

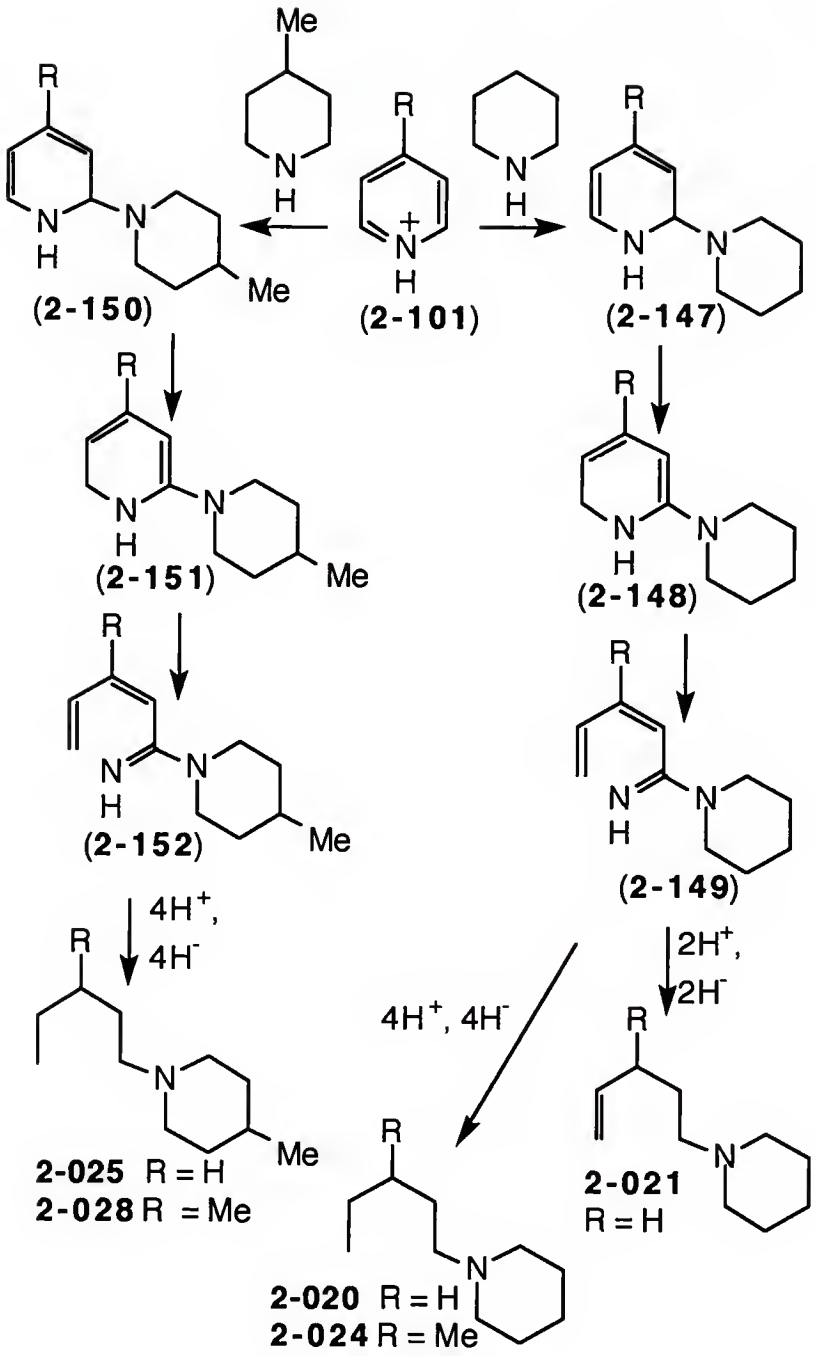
converts **2-145** into the saturated product **2-146**. We believe mechanisms of these types to be involved in the formation of products **2-020**, **2-024**, **2-025**, **2-028**, and **2-029** (Scheme 2-12).



Scheme 2-10



Scheme 2-11


Me
R
N
H
N
N
H
Me
(2-150)
R
+
N
H
(2-101)
N
H
R
N
H
N
(2-147)
R
N
H
N
(2-151)
Me
R
N
H
N
(2-148)
R
N
H
N
(2-152)
Me
R
N
H
N
(2-149)
4H+,
4H-
2H+,
2H-
4H+, 4H-
R
N
Me
2-025 R = H
2-028 R = Me
R
N
2-021
R = H
R
N
2-020 R = H
2-024 R = Me

Scheme 2-12

Conclusions

Formic acid variously acts as a formylating, methylating, reducing and oxidizing agent when it reacts with piperidine, pyridine and some of their methyl derivatives under aquathermolysis conditions. In similar reactions both piperidine and pyridine are converted to significant amounts of 1-alkylpiperidines, namely 1-methyl-, 1-ethyl-, 1-propyl- and 1-pentyl-piperidines. 1-(4-Methylpentyl)piperidine was not observed as product from the aquathermolyses. Through the use of isotropic labelling it has been demonstrated that only the 1-methyl- derivative originated from formic acid. That is, during the course of the reactions piperidine and pyridine were both formylated and then subsequently reduced to the 1-methyl derivatives. The 1-ethyl- and 1-propyl derivatives arise from the heterocyclic ring C-C bond fission by retro-vinylogous-bis-aza-Aldol reactions. These unique C-C bond scissions show for the first time that heterocyclic rings are susceptible to opening other than at the heteroatoms. Other reaction pathways elucidated during the course of this work include conventional formic acid reduction/formylation, addition to 2,3,4,5-tetrahydropyridinium cations and ring opening of isomers of products formed by addition of piperidines to a quaternized pyridinium cation.

It has been shown that formic acid at 350 °C converts pyridine and piperidine into a well defined mixture of specific *N*-alkylpiperidines. 4-Methylpyridine and 4-methylpiperidine are similarly converted into the corresponding 1-alkyl-4-methylpiperidines. It has been demonstrated that all the 1-alkyl groups (except for 1-methyl) arise from a second molecule of the heterocyclic ring compound and not from the formic acid. The formation of all products can be rationalized by addition of a piperidine molecule to a pyridine or di- or tetra-hydropyridine analog.

Many of the reactions proposed in the present work are the reverse of the commercially important pyridine ring-forming reaction from aldehydes and ammonia, and should help in better understanding of the latter. In principle, a very useful commercial

synthesis of pyridine involves the formation of the C_5 unit in situ by one or more base-catalyzed condensation reactions. With ammonia or an amine as the condensing agent, cyclization is usually spontaneous. On the industrial scale, self condensation of simple aldehydes with ammonia lead to a variety of pyridines [79MI64]. Perhaps, the mechanistic pathways may be viewed as cleavage into two molecules of aldehyde, the subsequent intermediate can enable retro-aldol cleavage of the pyridines.

Experimental

^1H NMR spectra were recorded either on a Varian VXR 300 (300 MHz) or a General Electric QE 300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) used as the internal standard. Coupling constants (*J* values) are reported in Hz. All Grignard reactions were run under an inert atmosphere using oven dried apparatus. Solvents and anhydrous liquid reagents were dried prior to use: diethyl ether was distilled over sodium benzophenone ketyl. Analytical thin layer chromatography (TLC) was perfomed using pre-coated silica gel 60 F_{254} plastic plates (0.2 mm thick) using iodine as indicator.

1-(Piperidinomethyl)benzotriazole (**2-033**) was prepared by applying the literature procedure [87JCS(P1)799]. Benzotriazole (5.0 g, 42 mmol) was dissolved in EtOH (50.0 mL). Next was added 37% aqueous formaldehyde (6.60 mL, 64.0 mmol) and piperidine (4.2 mL, 42.0 mmol) and the reaction was stirred vigorously at room temperature (18 h). Precipitation was induced by addition of H_2O (2 mL). The product obtained was washed with EtOH (25 mL) to yield a white solid (8.6 g, 94%) which was pure by ^1H NMR, and used in subsequent reactions: M.p. 88-90 °C (lit.[46JA2496] m.p. 92.5-93.5 °C). ^1H NMR ($CDCl_3$) : δ 1.3 (m, 2H) (piperidine), 1.6 (quintet, 4H, $J = 8.0$) (piperidine), 2.6 (t,

4H, J = 7.0) (piperidine), 5.43 (s, 2H) (CH_2), 7.4 (m, 1H) (Bt), 7.7 (d, 1H, J = 7.0) (Bt), 8.2 (d, 1H, J = 8.0) (Bt). ^{13}C NMR ($CDCl_3$) : δ 23.5, 25.7, 51.5, 70.1, 110.1, 118.2, 119.7, 123.7, 126.3, 127.3.

1-(*N*,*N*-Dimethylaminomethyl)benzotriazole (**2-034**) was prepared according to the literature procedure [92JOC4932]. Benzotriazole (5.13 g, 43 mmol) was dissolved in EtOH (42.0 mL). Next was added 37% aqueous formaldehyde (6.60 mL, 64.0 mmol). The mixture was stirred vigorously and cooled to 0 °C. After the initial precipitate formed, *N*,*N*-dimethylamine (6.4 mL, 129 mmol) was added dropwise *via* an addition funnel and the reaction was allowed to warm up to room temperature (18 h). Crystallization of the crude product was induced by cooling the mixture to -18 °C. The crude white solid was filtered and washed with EtOH (20 mL). Recrystallization from ethanol yielded white prisms (6.3 g, 83%): M.p. 95-97 °C (lit.[52JA3868] m.p. 99-100.5 °C). ^1H NMR ($CDCl_3$): δ 2.4 (s, 6H) ($2CH_3$), 5.4 (s, 2H) (CH_2), 7.4 (m, 1H) (Bt), 7.5 (t, 1H, J = 7.0) (Bt), 7.7 (d, 1H, J = 8.2) (Bt), 8.1 (d, 1H, J = 7.3) (Bt). ^{13}C NMR ($CDCl_3$) δ: 42.3, 69.8, 109.8, 119.5, 123.7, 127.3, 133.76, 145.5.

General procedure for the synthesis of *N*-alkylpiperidines

1-(2-Methylbutyl)piperidine (**2-019**). Mg metal (1.7 g, 69.2 mmol) was suspended with an iodine chip in Et_2O (20 mL). 2-Bromobutane (9.5 g, 69.4 mmol) was dissolved in Et_2O (50 mL) and added dropwise to the Mg metal. After the addition was complete, the mixture was heated under reflux and stirred for 0.5 h. 1-(Piperidinomethyl)benzotriazole (5.0 g, 23.0 mmol) was then added *via* a Soxhlet extractor. The reaction was then stirred and refluxed for 18 h. The reaction was cooled and quenched with a minimal amount of water (2 mL). The bulk of the Et_2O was decanted from the solid and the remainder filtered through celite. The Et_2O was dried ($MgSO_4$) and

removed *in vacuo* to yield a crude yellow oil, which was purified by Kugelrohr distillation. A colorless oil (2.20 g, 62%) was isolated: B.p. 65 °C/0.65 mm Hg; ^{1}H NMR ($CDCl_3$): δ 0.8 (d, 3H, J = 8.0) (CH_3), 0.9 (t, 3H, J = 8.0) (CH_3), 1.0-1.1 (m, 1H) (CH), 1.3-1.5 (m, 4H) ($2CH_2$ [ring]), 1.5-1.6 (quintet, 4H, J = 8.0) (CH_2 [ring]), 1.0-2.1 (d of d, 2H, J = 6.0, 8.0) (CH_2N [aliphatic]), 2.2-2.4 (br m, 4H) (CH_2N [ring]). ^{13}C NMR ($CDCl_3$): δ 11.3, 17.9, 24.6, 26.1, 27.9, 32.0, 55.1, 66.4. HR MS (70 eV, EI): *m/z* (%) 155.1666 (7) [M^+], 98 (100) [$C_5H_{11}N^+$]; $C_{10}H_{21}N$ requires 155.1674.

1-(3-Methylpentyl)piperidine (**2-024**). This product was obtained as a crude yellow oil and was purified by Kugelrohr distillation to give a colorless oil (3.0 g, 76%); B.p. 75 °C/0.75 mm Hg; ^{1}H NMR ($CDCl_3$): δ 0.8-0.9 (d & t, 6H, J = 8.0) ($2CH_3$), 1.1-1.2 (quintet, 1H, J = 8.0) (CH), 1.2-1.4 (m, 4H) ($2CH_2$ [aliphatic]), 1.4-1.5 (m, 2H) (CH_2 [ring]), 1.5 (quintet, 4H, J = 8.0) ($2CH_2$ [ring]), 2.2-2.3 (m, 2H) (CH_2N [aliphatic]), 2.3-2.4 (br s, 4H) (CH_2N [ring]); ^{13}C NMR ($CDCl_3$): δ 11.2, 19.3, 24.5, 26.0, 29.6, 33.3, 33.5, 54.7. HR MS (70 eV, EI): *m/z* (%) 169.1827 (7), [M^+], 98 (100) [$C_5H_{11}N^+$]; $C_{11}H_{23}N$ requires 169.1830.

1-(4-Methylpentyl)piperidine (**2-032**). This product was obtained as a crude yellow oil and was purified by Kugelrohr distillation to give a pale yellow oil (2.2 g, 57%); B.p. 65 °C/0.1 mm Hg; ^{1}H NMR ($CDCl_3$): δ 0.9 (d, 6H, J = 8.0) ($2CH_3$), 1.2 (quintet, 2H, J = 9.0) (CH_2), 1.5 (m, 4H) (piperidine), 1.5 (m, 4H) (piperidine), 2.3 (t, 2H, J = 7.0) (CH_2 [ring]), 2.4 (br. s, 3H) (aliphatic). ^{13}C NMR ($CDCl_3$): δ 22.2, 24.7, 25.8, 25.9, 36.8, 54.5, 59.8. HR MS (70 eV, EI): *m/z* (%) 169.1823 (9), [M^+], 98 (100) [$C_5H_{11}N^+$]; $C_{11}H_{23}N$ requires 169.1830.

General procedure for the synthesis of acyclic amines

N,*N*-Dimethylpentylamine (**2-009**). *n*-Butyl bromide (11.68 g, 85.2 mmol) was dissolved in Et_2O (65 mL) and added dropwise to Mg metal (2.05 g, 85.2 mmol) in the presence of an iodine chip. After the addition was complete, the mixture was heated under gentle reflux and stirred for 0.5 h. After this period of time, 1-(*N*,*N*-dimethylaminomethyl)benzotriazole (5.0 g, 28.4 mmol) was added *via* Soxhlet extractor. The mixture was stirred and refluxed for 18 h. The reaction was cooled and quenched with aqueous NaOH (30 mL). The bulk of the Et_2O was decanted from the solid and the remainder filtered through celite, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil - GC yield 79%. The crude product was purified by Kugelrohr distillation to give a colorless oil (27%): B.p. 55 °C/0.9 mm Hg (lit. [46MI165] b.p. 122-123 °C/760 mm Hg). ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 6.0) (CH_3), 1.50-1.60 (m, 6H) ($3CH_2$), 2.20 (s, 6H) ($2CH_3N$), 2.30 (d, 2H, J = 6.0) (CH_2N). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.5, 27.1, 29.6, 45.2, 59.7. HR MS (70 eV, EI): *m/z* (%) 115.1364 (8%) [M^+], 98 (100) [$C_5H_{11}N^+$]; $C_7H_{17}N$ requires 115.1361.

N,*N*-Dimethyl-2-methylpentylamine (**2-013**). This product was obtained crude as a yellow oil which was purified by Kugelrohr distillation to give a colorless oil (1.02 g, 28%): B.p. 75 °C/2 mm Hg (lit.[50CCC512] b.p. 134 °C/760 mm Hg). ^{1}H NMR ($CDCl_3$): δ 0.7-0.8 (t, 3H, J = 6.0) (CH_3 [terminal]), 0.9 (d, J = 6.0)3H) (CH_3), 1.02-1.1 (q, 1H, J = 6.0) (CH_a), 1.2 (d, 1H, J = 6.0) (CH_b), 1.3-1.4 (m, 2H) (CH_2), 1.7-1.8 (m, 1H) (CH [CH_3]), 2.3-2.4 (d of d, 6H, J = 6.0, 6.0) (CH_2N), 2.4 (s, 6H) ($2CH_3N$). ^{13}C NMR ($CDCl_3$): δ 14.3, 18.2, 20.1, 30.8, 37.8, 45.9, 67.4. HR MS (70 eV, EI): *m/z* (%) 129.1529 (7) [M^+], 98 (100) [$C_5H_{11}N^+$]; $C_8H_{19}N$ requires 129.1517.

Aquathermolysis: General[2.7]

All starting materials were checked by GC prior to use; where necessary they were purified to >98%. 49% Aqueous formic acid was deoxygenated with argon for 1 h prior to use. The model compound (1 g) and the formic acid (7 mL) were charged into a nitrogen-blanketed 1" Swagelok stainless steel bomb (plug and cap) which was then sealed. The reactor was then kept, without agitation, in a fluidized sand bath (model SBS-4) set at 350 °C using a Techne temperature controller (TC-8D) for the specified time period. The temperature profile was measured by a Barnant 115 thermocouple thermometer (type J) placed in the sandbath adjacent to the reaction vessel. After the reaction period, the reactor was immediately cooled with a stream of cold air and then quenched in dry ice. The reaction mixture was then worked up as previously described [90EF493], and subjected to GC analyses on a Hewlett Packard 5890 instrument (flame ionization detector, [FID]) with a 15 m capillary column (SPB-1) and a temperature program of 10 °C min^{-1} from 50-250 °C. GC/MS analyses of all compounds were performed on a Varian 3400 gas chromatograph and a Finnigan MAT 700 ion trap detector.

Product identification. The GC behavior of all the compounds in this chapter (starting material and products) are collated in Table 2-1 (in the format as explained in earlier papers [90EF493]). Within the reaction mixtures, the identities of all the starting materials and some of their reaction products [**2-001**--**2-005**, **2-007**--**2-013**, **2-019**, **2-023**, **2-024**, **2-026**] were confirmed by direct comparisons of retention times and mass spectral fragmentation patterns with those of the authentic compounds, under essentially the same mass spectral operating conditions. Table 2-2 records the major features of the mass spectra together with a literature reference to the MS of the compounds (where available). Table 2-3 records the mass spectral fragmentation patterns of products (**2-017**, **2-020**) which were identified by comparison with published MS data. In such cases the source of

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2.7 All aquathermolyses were conducted jointly by Marudai Balasubramanian, Richard A. Barcock, and Elena S. Ignatchenko at the University of Florida.

the reference spectrum is always given and the major features of both the experimental and the reference spectrum are recorded. Table 2-4 records the MS patterns of products [**2-006**, **2-014**--**2-016**, **2-018**, **2-021**, **2-022**, **2-025**, **2-027**--**2-031**] for which no published MS data could be found. These products were assigned from their MS fragmentation patterns, together with a consideration of the reaction conditions, starting materials, and a reasonable mechanistic pathway for their formation from the starting materials. Also, the mass spectral fragmentation patterns for the synthesized compounds (see Appendix A) **2-009**, **2-013**, **2-019**, and **2-024** are represented.

CHAPTER III
REACTION OF VARIOUS ALIPHATIC AMINES WITH FORMIC ACID: 1-OCTYLAMINE, DI-1-OCTYLAMINE, N,N-DIMETHYL-1-OCTYLAMINE, 1-DODECYLAMINE AND N,N-DIMETHYL-1-DODECYLAMINE

Introduction

As stated in Chapter II, nitrogen is among the heteroatoms found in coals [92EF439]. Due to the deleterious effects of N impurities (as mentioned in Chapter II), remaining in synthetic oils it is highly economical to remove them easily and cost effectively. Normal modes of purification involve denitrogenation and hydrodenitrogenation [92EF439, 93TL4739]. Aquathermolysis, the thermal transformation of organic compounds in aqueous environments, holds potential economic incentive as an alternative purification method for the conversion and purification of fossil fuels such as coal.[3.1]

Denitrogenation can be a costly process for the removal of nitrogen form heterocyclic nitrogen containing compounds due to the large excess of hydrogen needed to afford hydrogenolysis of the heterocyclic ring (as mentioned in Chapter II), but aliphatic amines should undergo denitrogenation quite rapidly since there is no need to use excess hydrogen. With six-membered heterocycles, progressive decarboxylation and C-C, C-N bond cleavages occur, leading to the generation of alkane chains [92EF439]. The aliphatic amine already contains the alkane chain, and would therefore undergo fragmentation

3.1 This project formed part of a joint collaboration between the Katritzky Research Group at the University of Florida and groups at Exxon Research and Engineering Co.

directly. There would be no need for significant prehydrogenation of the system. Aliphatic amines are among the nitrogen compounds found in petroleum or synthetic oils.

Our main objective was to uncover the general pattern of reactivity under aquathermolysis[3.2,3.3] conditions of some common, naturally occurring amine-related functional groups. Literature reports have shown that formic acid at temperatures ranging from 100 - 200 °C, readily reduces basic *N*-heterocyclic rings. Thus pyridine, quinoline, isoquinoline and acridine can be easily reduced to piperidine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, and 9,10-dihydroacridine respectively. The analogous salts yield the corresponding *N*-substituted compounds [65CCC1700, 65CLI1058, 55ZOK1947, 57ZOK3021]. More recently, it has been demonstrated in our laboratories that formic acid induces the hydrogenation of the pyridine ring and subsequently leads to its scission [93TL4739].

As previously stated, it was demonstrated in our laboratories [93TL4739] that in 49% aqueous formic at 350 °C pyridine was converted predominantly into 1-formylpiperidine accompanied by several *N*-alkylpiperidines as minor products. In connection with the elucidation of the mechanism for the formation of the *N*-alkylpiperidines, we have also studied the effect of 49% aqueous formic acid on representative primary [1-octylamine (**3-008**)[3.4], 1-dodecylamine (**3-023**)], secondary [di-1-octylamine (**3-033**)] and tertiary [*N*,*N*-dimethyl-1-octylamine (**3-013**), *N*,*N*-dimethyl-1-dodecylamine (**3-028**)] alkylamines (Scheme 3-1).

3.2 All synthetic work and mass spectral investigations / interpretations were performed by Rolsyn L. White at the University of Florida.

3.3 All aquathermolysis reactions were conducted by Elena S. Ignatchenko at the University of Florida.

3.4 Compounds have been numbered sequentially according to their retention times with compound **3-001** bearing the lowest retention time (see Table 3-1 for a complete listing). Compound numbers equal to or greater than **3-100** are used for postulated intermediates not detected by the GC/MS analyses.

$C_8H_{17}NH_2$	$C_8H_{17}NMe_2$	$C_{12}H_{25}NH_2$	$C_{12}H_{25}NMe_2$	$(C_8H_{17})_2NH$
3.008	**3.013**	**3.023**	**3.028**	**3.033**

Scheme 3-1

The gas chromatographic (GC) behavior of all the compounds employed for this study and the products are recorded in Table 3-1.[3.5] Table 3-2, 3-3 and 3-4 contain the compiled mass spectral data for the analysis of results. Table 3-2 contains the sources and purities of the starting materials used and have been compiled based upon the direct comparison of the GC retention times and of the mass spectral (MS) fragmentation pattern with those of the authentic compound. Table 3-3 contains compounds which have been identified by comparison of MS patterns with literature MS data for the same compound. Those compounds for which no suitable literature MS data were available have been identified by their MS fragmentation patterns (obtained from the aquathermolysis runs) and have been compiled in Table 3-4. A more detailed explanation of Tables 3-2--3-4 is given in section 3.5 Experimental. The results from the aquathermolyis of each amine are collected in Tables 3-5--3-11. All product yields (molar %) are represented as a percentage of moles as described in detail previously [90EF493] and have been corrected with regard to their response factors [89TCM17].[3.6]

Structures and proposed reaction pathways for the formation of these products are given in Schemes 3-6--3-9 (see section 3.4 Discussion). In these reaction Schemes, numbers ≥ **3-100** are used for postulated intermediates not detected by the GC/MS analyses.

3.5 The data has been compiled as explained in this paragraph according to the series of aquathermolysis papers [90EF499].

3.6 Knowledge of the response factor allows quantitative analysis of complex product mixtures by GC/MS - especially for those cases where some or all of the products are unavailable.

Table 3-1. Structure and Identification of Starting Materials and Products

No.	t_R(min)	Compound	MW	Eq. W	Basis[a]	Factor[b]
3-001	3.68	*N,N*-dimethyl-1-butylamine	101	101	Table 3-2	0.72
3-002	4.96	1-hexanol	102	102	Table 3-3	0.79
3-003	5.49	*N,N*-dimethy-1-hexylamine	129	129	Table 3-2	0.71
3-004	6.39	*N*-methyldi-1-butylamine	143	71.5	Table 3-4	0.70
3-005	7.40	2-octanone	128	128	Table 3-2	0.78
3-006	7.90	*N,N*-dimethyl-2-ethyl-1-hexylamine	157	157	Table 3-3	0.70
3-007	8.01	*N*-methyl-*N*-1-butylformamide	115	115	Table 3-4	0.50
3-008	8.33	1-octylamine	129	129	Table 3-2	0.71
3-009	8.59	*N,N*-dimethyl-3-octylamine	157	157	Table 3-3	0.70
3-010	8.86	1-octanol	130	130	Table 3-2	0.78
3-011	9.06	*N*-methyl-3-octylamine	143	143	Table 3-4	0.70
3-012	9.23	*N*-methyl-1-octylamine	143	143	Table 3-3	0.70
3-013	9.35	*N,N*-dimethyl-1-octylamine	157	157	Table 3-2	0.70
3-014	9.94	tri-1-butylamine	185	61.7	Table 3-3	0.69
3-015	10.73	1-dodecene	168	168	Table 3-3	0.94
3-016	10.87	dodecane	170	170	Table 3-2	0.94
3-017	10.94	2-dodecene	168	168	Table 3-3	0.94
3-018	11.03	*N*-methyl-*N*-1-hexylformamide	143	143	Table 3-4	0.49
3-019	11.10	3-dodecene	168	168	Table 3-3	0.94
3-020	11.57	*N,N*-di-1-butylformamide	157	78.5	Table 3-3	0.49
3-021	12.06	*N*-methyldi-1-hexylamine	199	99.5	Table 3-4	0.68
3-022	14.52	*N*-1-octylformamide	157	157	Table 3-3	0.49
3-023	14.64	1-dodecylamine	185	185	Table 3-2	0.69
3-024	14.84	*N*-methyl-*N*-1-octylformamide	171	171	Table 3-4	0.48
3-025	14.91	*N*-1-octylacetamide	171	171	Table 3-4	0.69
3-026	15.06	1-dodecanol	186	186	Table 3-2	0.63
3-027	15.18	*N*-methyl-1-dodecylamine	199	199	Table 3-4	0.68
3-028	15.37	*N,N*-dimethyl-1-dodecylamine	213	213	Table 3-2	0.68
3-029	15.71	*N*-methyl-*N*-1-octylacetamide	185	185	Table 3-4	0.69
3-030	16.75	*N*-acetyl-*N*-1-octylformamide	199	199	Table 3-4	0.31
3-031	17.41	*N*-1-octyl-*N*-3-octylamine	241	120.5	Table 3-4	0.67

Table 3-1 continued

No.	t_R(min)	Compound	MW	Eq. W	Basis[a]	Factor[b]
3-032	18.12	*N*-methyldi-1-octylamine	255	127.5	Table 3-3	0.66
3-033	18.41	di-1-octylamine	241	120.5	Table 3-2	0.67
3-034	18.76	*N*-1-octyl-*N*-3-octylformamide	269	134.5	Table 3-4	0.45
3-035	19.54	*N*-1-dodecylformamide	213	213	Table 3-2	0.47
3-036	19.99	*N*-methyl-*N*-1-dodecylformamide	227	227	Table 3-4	0.47
3-037	20.56	*N*-methyl-*N*-1-dodecylacetamide	241	241	Table 3-4	0.67
3-038	21.43	*N*-acetyl-*N*-1-dodecylformamide	255	255	Table 3-4	0.29
3-039	21.44	*N*-methyl-*N*-3-octyl-1-octylamine	255	127.5	Table 3-4	0.66
3-040	22.37	*N*,*N*-di-1-octylformamide	269	134.5	Table 3-3	0.45
3-041	22.62	*N*,*N*-di-1-octylacetamide	283	141.5	Table 3-3	0.65
3-042	24.58	tri-1-octylamine	353	117.7	Table 3-3	0.63
3-043	28.91	*N*-methyldi-1-dodecylamine	367	183.5	Table 3-4	0.61
3-044	29.26	di-1-dodecylamine	353	176.5	Table 3-3	0.63

t_R(min) = Retention time in minutes. MW = molecular weight. Eq. W = equivalent weight. a = Identification Basis, see appropriate table. b = Response Factor, see ref [89TCM17].

Table 3-2. Properties of Authentic Compounds used as Starting Materials and for the Identification of Products

No.	Compound	MW	a	Purity (%)	m/z (% relative intensity)	Ref. Spectra#
3-001	*N,N*-dimethyl-1-butylamine	101	A	99	101(9); 72(1); 58(100); 44(5); 42(12)	118158
3-003	*N,N*-dimethyl-1-hexylamine	129	A	99	129(7); 114(1); 84(1); 58(100); 42(9)	6209
3-005	2-octanone	128	K	97	128(12); 113(5); 85(9); 58(96); 43(100)	120848
3-008	1-octylamine	129	A	>99	129(2); 100(3); 86(5); 58(6); 45(8); 41(10); 30(100)	120973
3-010	1-octanol	130	A	97	112(2); 84(43); 83(46); 70(69); 56(100); 55(89)	121161
3-013	*N,N*-dimethyl-1-octylamine	157	A	95	157(6); 143(2); 59(4); 58(100); 44(41); 42(6)	c
3-016	dodecane	170	A	99	170(8); 85(46); 71(64); 57(100); 56(22); 55(18)	126002
3-023	1-dodecylamine	185	F	99	185(2); 184(1); 55(9); 44(10); 43(10); 41(15); 30(100)	28046
3-026	1-dodecanol	186	A	98	168(1); 140(8); 97(43); 83(65); 69(81); 55(100)	127402
3-028	*N,N*-dimethyl-1-dodecylamine	213	A	97	213(4); 212(1); 84(2); 59(4); 58(100)	40885
3-033	di-1-octylamine	241	A	>99	241(5); 143(10); 142(100); 57(7); 56(4); 44(36)	53027
3-035	*N*-1-dodecylformamide	213	S	100	213(18); 184(15); 72(39); 59(100); 58(68); 44(19)	34318
3-042	tri-1-octylamine	353	A	98	353(2); 352(2); 256(2); 255(19); 254(100); 156(8)	135035

a A = Aldrich, F = Fluka, K = Eastman Kodak; L = Lancaster, S = synthesized authentic compound (see experimental section). b = spectral numbers of the mass spectral data for the compounds found from a search of the Wiley.138L / MSP. c = no spectra available.

Table 3-3. Identification of Products by Comparison of Mass Spectral Fragmentation with Literature Data

No.	Compound	MW	Fragmentation Found m/z (% relative intensity)	Ref.[a] Spectra#	Fragmentation Reported m/z (% relative intensity]
3-002	1-hexanol	102	84(6); 69(33); 56(100); 55(53); 43(48)	1451	84(12); 69(33); 56(100); 55(51); 43(52)
3-006	*N*,*N*-dimethyl-2-ethyl-1-hexylamine	157	157(4); 84(3); 59(4); 58(100); 42(4)	124621	157(3); 84(2); 59(4); 58(100); 42(3)
3-009	*N*,*N*-dimethyl-3-octylamine	157	157(3); 128(85); 86(100); 71(11); 42(8)	15823	157(2); 128(64); 86(100); 71(12); 42(16)
3-012	*N*-methyl-1-octylamine	143	143(7); 55(3); 44(100); 42(5); 41(7)	10397	143(1); 55(2); 44(100); 42(3); 41(6)
3-014	tri-1-butylamine	185	185(5); 142(100); 100 (44); 58(10); 44(12)	127292	185(7); 142(100); 100(46); 58(12); 44(43)
3-015	1-dodecene	168	168(33); 83(66); 70(71); 69(84); 55(100)	20662	168(9); 83(32); 70(50); 69(67); 55(100)
3-017	2-dodecene	168	168(47); 83(53); 70(95); 56(63); 55(100)	20664	168(7); 83(36); 70(57); 56(75); 55(100)
3-019	3-dodecene	168	168(7); 70(81); 69(87); 56(82); 55(100)	20666	168(11); 70(68); 69(96); 56(87); 55(100)
3-020	*N*,*N*-di-1-butylformamide	157	157(3); 72(100); 114(59); 58(13); 44(21)	15804	157(1); 114(50); 72(100); 58(13); 44(15)
3-022	*N*-1-octylformamide	157	157(3); 100(49); 59(88); 58(100); 30(76)	15802	157(4); 100(24); 59(79); 58(92); 30(100)
3-032	*N*-methyldi-1-octylamine	255	255(3); 157(12); 156(100); 58(24); 44(7)	58578	255(1); 157(12); 156(100); 58(33); 44(11)
3-040	*N*,*N*-di-1-octylformamide	269	269(2); 198(5); 171(13); 170(100); 72(54)	63194	269(2); 198(5); 171(13); 170(100); 72(54)
3-041	*N*,*N*-di-1-octylacetamide	283	283(2); 184(59); 170(40); 142(100); 44(18)	68137	283(3); 184(52); 170(12); 142(100); 44(26)
3-044	di-1-dodecylamine	353	353(1); 199(15); 198(100); 44(14)	88747	353(2); 199(17); 198(100); 44(32)

a = spectral numbers of the mass spectral data for the compounds from a search of the Wiley138.L / MSP.

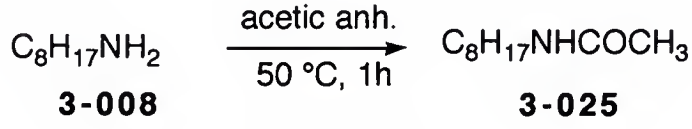
Table 3-4. Identification of Products From Mass Spectral Fragmentation Patterns

No	Compounds	MW	Fragmentation Pattern [% relative intensity; structure of fragment ion
3-004	*N*-methyldi-1-butylamine	143	143(9, M^+); 100(79, M-C_3H_7); 58(100, M-C_6H_{13}); 42(23)
3-007	*N*-methyl-*N*-1-butylformamide	115	115(10, M^+); 114(17, M-H); 73(22, M-C_3H_6); 72(71, M-C_3H_7); 44(100; M-C_3H_7CO); 42(23)
3-011	*N*-methyl-3-octylamine	143	143(1, M^+); 142(10, M-H); 73(5, M-C_5H_{10}); 72(100, M-C_5H_{11}); 44(3); 28(17)
3-018	*N*-methyl-*N*-1-hexylformamide	143	143(10, M^+); 142(15, M-H); 73(35, M-C_5H_{10}); 72(100, M-C_5H_{11}); 44(92); 42(21)
3-021	*N*-methyldi-1-hexylamine	199	199(4, M^+); 198(1, M-H); 128(100, M-C_5H_{11}); 58(70, M-$C_{10}H_{21}$); 42(21)
3-024	*N*-methyl-*N*-1-octylformamide	171	171(8, M^+); 156(7, M-CH_3); 115(3); 86(10); 73(40, M-C_7H_{14}); 72(100, M-C_7H_{15}); 44(42)
3-025	*N*-1-octylacetamide	171	171(18, M^+); 156(15, M-CH_3); 128(16); 100(42); 73(90); 72(93, M-C_7H_{15}); 30(100)
3-027	*N*-methyl-1-dodecylamine	199	199(5, M^+); 198(1, M-H); 184(1,); 170(1); 58(91, M-$C_{10}H_{21}$); 44(100, M-$C_{11}H_{23}$); 30(8)
3-029	*N*-methyl-*N*-1-octylacetamide	185	185(6, M^+); 184(7, M-H); 156(10); 100(21); 114(13); 86(100, M-C_7H_{15}); 58(36); 30 (18)
3-030	*N*-acetyl-*N*-1-octylformamide	199	199(3, M^+); 198(2, M-H); 100(95); 184(3, M-CH_3); 170(100, M-HCO); 114(11); 58(11)
3-031	*N*-1-octyl-*N*-3-octylamine	241	241(2, M^+); 226(8, M-CH_3); 157(2, M-C_6H_{12}); 156(100, M-C_6H_{13}); 142(65, M-C_7H_{15})
3-034	*N*-1-octyl-*N*-3-octylformamide	269	269(1, M^+), 268(1, M-H); 171(13, M-C_7H_{14}); 170(100, M-C_7H_{15}); 156(12);72(17)
3-036	*N*-methyl-*N*-1-dodecylformamide	227	227(7; M^+); 226(13, M-H); 212(11, M-CH_3); 100(10); 114(13); 86(13); 72(100, M-$C_{11}H_{23}$)
3-037	*N*-methyl-*N*-1-dodecylacetamide	241	241(6, M^+); 240(8, M-H); 213(13, M-CO), 212(13); 100(14); 73(28); 58(37); 30(10)
3-038	*N*-acetyl-*N*-1-dodecylformamide	255	255(2, M^+); 254(2, M-H); 226(100, M-HCO); 114(10); 100(71); 72(38)
3-039	*N*-methyl-*N*-3-octyl-1-octylamine	255	255(15, M^+); 226(18, M-Et); 212(19); 198(25, M-C_4H_9); 184(100, M-C_5H_{11}); 156(55)
3-043	*N*-methyldi-1-dodecylamine	367	367(2, M^+); 366(3, M-H); 213(16, M-$C_{11}H_{22}$); 212(100, M-$C_{11}H_{23}$); 198(1)

Synthesis of Compounds

After extensive mass spectral interpretation and subsequent identification of all the products/unknowns obtained from the aquathermolysis runs there were several compounds whose formation remained obscure. Therefore, five compounds were selected to be synthesized. They included *N*-1-octylacetamide (**3-025**) *N*, *N*-dimethyl-3-octylamine (**3-009**), *N*, *N*-dimethyl-2-octylamine (**3-045**), 2-dodecylamine (**3-049**) and 3-dodecylamine (**3-050**). Amine **3-025** was chosen because it appeared to be an unlikely product based upon the expected reaction pathways, while amines **3-009** and **3-045** were chosen because no direct mechanistic pathway for their formation could be suggested. The primary amines (**3-049**, **3-050**) were synthesized to investigate whether or not amination of the alkenes formed during aquathermolysis was occurring.

N-1-Octylacetamide (**3-025**) was synthesized using 1-octylamine (**3-008**) and acetic anhydride and was isolated as a clear oil in 68% yield (Scheme 3-2). Analysis of the MS fragmentation pattern of our authentic *N*-1-octylacetamide (**3-025**) shows that its pattern is identical to that of the literature (see Table 3-3) and suggests that amide **3-025** could be a product from the aquathermolysis of 1-octylamine (**3-008**).

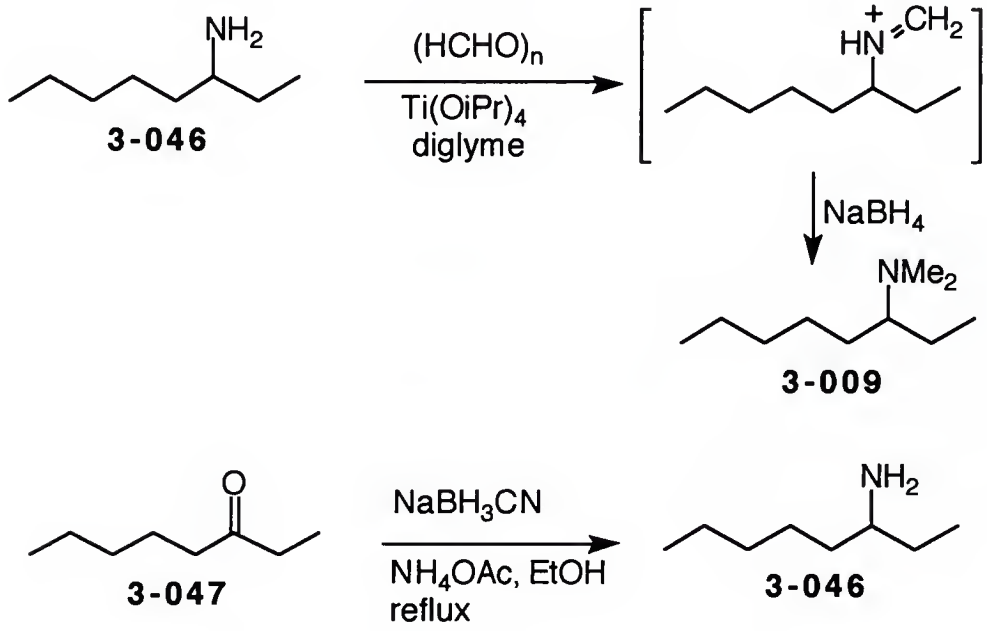


3-008 **3-025**

Scheme 3-2

N, *N*-Dimethyl-3-octylamine (**3-009**) was synthesized using a literature method [94TL2401]. This method uses titanium (IV) isopropoxide [Ti(OiPr)4] and sodium borohydride ($NaBH_4$) for the reductive amination of formaldehyde with 3-octylamine (**3-046**). One equivalent of amine and two equivalents of Ti(OiPr)4 are allowed to reflux in diglyme. The corresponding imine is then reduced with sodium borohydride ($NaBH_4$). It

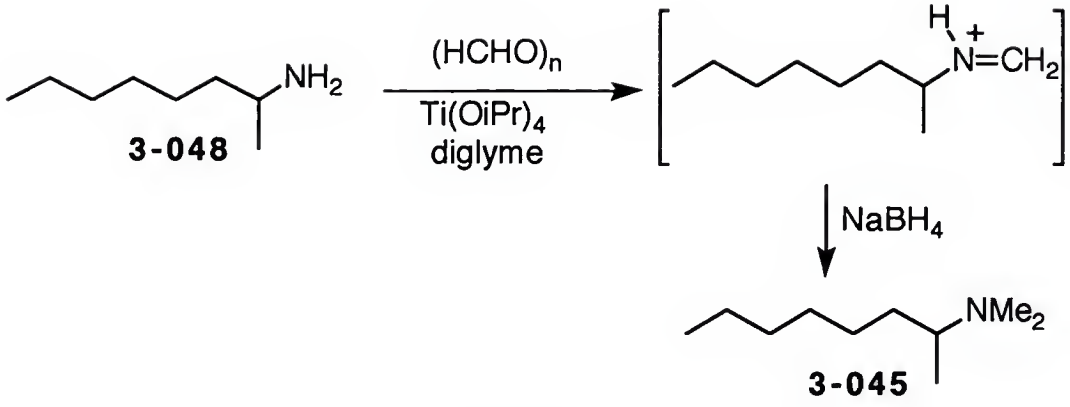
is thought that the $Ti(OiPr)_4$ functions as a Lewis acid catalyst as well as a water scavenger (Scheme 3-5). 3-Octylamine (**3-046**) was prepared from the corresponding ketone, 3-octanone (**3-047**) using the literature method [83JCS(P1)3027] (Scheme 3-3).



Scheme 3-3

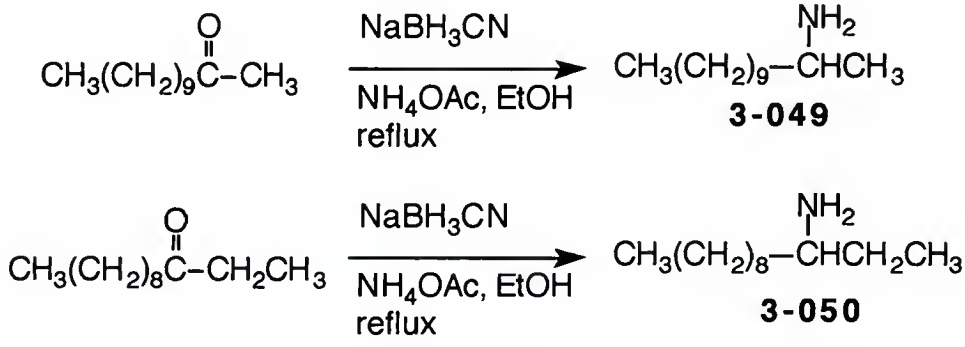
Mass spectral analysis of the authentic *N,N*-dimethyl-3-octylamine (**3-009**) revealed that the MS fragmentation pattern is identical to that of the literature (see Table 3-3) and suggests that amine **3-009** could be a product from *N,N*-dimethyl-1-octylamine (**3-013**). The proposed compound (i.e. from the fragmentation found in the aquathermolysis runs), the library match and the synthesized compound are identical (see Table 3-3).

N,N-Dimethyl-2-octylamine (**3-045**) was also synthesized using the above literature procedure [94TL2401] from 1-methylheptylamine (**3-048**) (Scheme 3-4). It was suggested that the compound proposed to be *N,N*-dimethyl-2-ethyl-1-hexylamine (**3-006**) may have been wrongly identified and that it might actually be *N,N*-dimethyl-2-octylamine (**3-045**). Unfortunately, the mass spectral interpretation of the authentic **3-045** could not prove this hypothesis.



Scheme 3-4

2-Dodecylamine (**3-049**) and 3-dodecylamine (**3-050**) were synthesized from the corresponding 2- and 3-dodecanone using a literature method [83JCS(P1)3027] (Scheme 3-5). As with amine **3-046**, the ketone is reductively aminated to the corresponding amine. These primary amines were synthesized to tell whether the 2-dodecene (**3-017**) and 3-dodecene (**3-019**) formed (see section 3.3 Results) were being converted back to the corresponding amines. This hypothesis was disproven, as neither of the amines (**3-049** nor **3-050**) were observed as products. Further discussion of these and the above compounds will be covered in the Discussion (section 3.4).



Scheme 3-5

Results

1-Octylamine (**3-008**) (Table 3-5). The reaction of 1-octylamine (**3-008**) with 49% aqueous formic acid (HCO_2H) at 350 °C for 0.5 h showed a 50.4% conversion to the major products *N*-1-octylformamide (**3-022**, 17.5%), and di-1-octylamine (**3-033**, 11.6%). Other minor products included 1-octanol (**3-010**, 2.7%), *N*-methyl-1-octylamine (**3-012**, 5.4%), *N*-methyl-*N*-1-octylformamide (**3-024**, 3.0%), *N*-1-octylacetamide (**3-025**, 4.2%), *N*-methyldi-1-octylamine (**3-032**, 1.0%) and *N*,*N*-di-1-octylformamide (**3-040**, 3.7%). *N*,*N*-Dimethyl-1-octylamine (**3-013**, 0.3%), *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**, 0.5%) and tri-1-octylamine (**3-042**, 0.5%) were formed in trace amounts. Extending the reaction time to 2 h resulted in a 60.1% conversion with *N*-1-octylformamide (**3-022**, 10.4%), di-1-octylamine (**3-033**, 23.7%), *N*,*N*-di-1-octylformamide (**3-040**, 7.9%) and tri-1-octylamine (**3-042**, 2.7%) as the major products. Similar minor and trace products were observed as in the 0.5 h reaction.

Reactions at lower temperature gave significant formamide product formation. At 250 °C in 49% aqueous HCO_2H for 0.5 h 1-octylamine (**3-008**) underwent a 98.1% conversion to products with *N*-1-octylformamide (**3-022**, 91.5%) as the major product along with *N*-methyl-*N*-1-octylformamide (**3-024**, 4.5%) and *N*-1-octylacetamide (**3-025**, 2.1%). Increasing the reaction time to 2 h gave a somewhat lower conversion (90.9%) to the major products *N*-1-octylformamide (**3-022**, 68.5%), *N*-methyl-*N*-1-octylformamide (**3-024**, 9.8%) and *N*-1-octylacetamide (**3-025**, 5.6%). *N*,*N*-Dimethyl-1-octylamine (**3-013**), *N*-acetyl-*N*-1-octylformamide (**3-030**) and *N*,*N*-di-1-octylformamide (**3-040**) were each observed in less than 2%. 1-Octanol (**3-010**), *N*-methyl-*N*-1-octylacetamide (**3-029**) and di-1-octylamine (**3-033**) were each observed in trace amounts. A similar trend in conversion was seen after 10 h where there was an 86.5% product conversion. The 10 h reaction gave *N*-1-octylformamide (**3-022**, 34.1%),

Table 3-5. Products from 1-Octylamine (**3-008**), 49% HCO_2H

Temp.(°C)					250			350
Time (h)				0.5	2	10	0.5	2
No.	Compound	MW	Identification					
3-008	1-octylamine	129	Table 3-2	1.9	9.1	13.5	49.6	39.9
3-010	1-octanol	130	Table 3-2	-	0.7	2.8	2.7	3.7
3-012	*N*-methyl-1-octylamine	143	Table 3-3	-	-	1.8	5.4	4.2
3-013	*N*, *N*-dimethyl-1-octylamine	157	Table 3-2	-	1.6	3.3	0.3	0.3
3-022	*N*-1-octylformamide	157	Table 3-3	91.5	68.5	34.1	17.5	10.4
3-024	*N*-methyl-*N*-1-octylformamide	171	Table 3-4	4.5	9.8	10.5	3-00	1.6
3-025	*N*-1-octylacetamide	171	Table 3-4	2.1	5.6	4.7	4.2	3.4
3-029	*N*-methyl-*N*-1-octylacetamide	185	Table 3-4	-	0.9	0.4	-	-
3-030	*N*-acetyl-*N*-1-octylformamide	199	Table 3-4	-	1.3	-	-	-
3-032	*N*-methyldi-1-octylamine	255	Table 3-3	-	-	2.6	1.0	1.7
3-033	di-1-octylamine	241	Table 3-2	-	0.4	9.7	11.6	23.7
3-039	*N*-methyl-*N*-3-octyl-1-octylamine	255	Table 3-4	-	0.7	1.0	0.5	0.6
3-040	*N*, *N*-di-1-octylformamide	269	Table 3-3	-	1.4	15.0	3.7	7.9
3-042	tri-1-octylamine	353	Table 3-2	-	-	0.6	0.5	2.7

N-methyl-*N*-1-octylformamide (**3-024**, 10.5%), di-1-octylamine (**3-033**, 9.7%) and *N*,*N*-di-1-octylformamide (**3-040**, 15.0%) as major products. A similar slate of minor products as seen previously was also observed.

The product slate suggests that formylation of **3-008** yields *N*-1-octylformamide (**3-022**) which can subsequently undergo reduction to furnish *N*-methyl-1-octylamine (**3-012**). Similarly, *N*,*N*-dimethyl-1-octylamine (**3-013**) can be derived from *N*-methyl-1-octylamine (**3-012**), but this conversion appears to occur in small amounts. Di-1-octylamine (**3-033**) can be obtained by further reaction of **3-013** with 1-octylamine (**3-008**). Reaction of di-1-octylamine (**3-033**) with HCO_2H leads to *N*,*N*-di-1-octylformamide (**3-040**) which can be subsequently reduced to *N*-methyldi-1-octylamine (**3-032**). Tri-1-octylamine (**3-042**) can be obtained by reaction of **3-033** with **3-013**.

The increasing amount of 1-octylamine (**3-008**) remaining with increasing reaction time and temperature is unexpected. Since reaction at 250 °C 0.5 h indicates 98.1% conversion, it appears that with increasing time and temperature all the 1-octylamine (**3-008**) is converted to the observed products, some of which revert to starting material.

Di-1-octylamine (**3-033**) (Table 3-6). After 0.5 h, the reaction of di-1-octylamine (**3-033**) with 49% aqueous HCO_2H at 350 °C showed 75.5% conversion to 1-octylamine (**3-008**, 3.9%), 1-octanol (**3-010**, 2.4%), *N*-methyldi-1-octylamine (**3-032**, 6.0%), *N*,*N*-di-1-octylformamide (**3-040**, 18.5%) and tri-1-octylamine (**3-042**, 38.5%). *N*-Methyl-1-octylamine (**3-012**), *N*-1-octylformamide (**3-022**), *N*-methyl-*N*-1-octylformamide (**3-024**) and *N*,*N*-di-1-octylacetamide (**3-041**) were formed in less than 2%. Trace amounts of *N*,*N*-dimethyl-1-octylamine (**3-013**) and *N*-1-octyl-*N*-3-octylformamide (**3-034**) were observed. Heating with 49% HCO_2H for 2 h led to the formation of 1-octylamine (**3-008**, 5.4%), 1-octanol (**3-010**, 5.4%), *N*-methyldi-1-octylamine (**3-032**, 6.2%), *N*,*N*-di-1-octylformamide (**3-040**, 14.7%) and tri-1-octylamine (**3-042**, 42.9%). *N*-Methyl-1-octylamine (**3-012**), *N*-1-octylformamide (**3-022**), *N*-methyl-*N*-1-octylformamide (**3-024**) and *N*,*N*-di-1-octylacetamide (**3-041**)

Table 3-6. Products from Di-1-octylamine (**3-033**), 49% HCO_2H

Temp.(°C)					250			350
Time (h)				0.5	2	10	0.5	2
No.	Compound	MW	Identification					
3-008	1-octylamine	129	Table 3-2	0.2	0.1	0.2	3.9	5.4
3-010	1-octanol	130	Table 3-2	-	<0.1	0.7	2.4	5.4
3-012	*N*-methyl-1-octylamine	143	Table 3-3	-	-	-	1.1	1.5
3-013	*N*, *N*-dimethyl-1-octylamine	157	Table 3-2	0.5	<0.1	0.5	<0.1	<0.1
3-022	*N*-1-octylformamide	157	Table 3-3	-	0.7	1.3	1.7	1.9
3-024	*N*-methyl-*N*-1-octylformamide	171	Table 3-4	-	0.6	2.0	1.5	1.9
3-029	*N*-methyl-*N*-1-octylacetamide	185	Table 3-4	-	<0.1	0.1	-	-
3-032	*N*-methyldi-1-octylamine	255	Table 3-3	6.8	10.0	9.3	6.0	6.2
3-033	di-1-octylamine	241	Table 3-2	6.9	11.7	18.7	24.3	18.1
3-034	*N*-1-octyl-*N*-3-octylformamide	269	Table 3-4	0.3	1.2	1.5	0.8	0.8
3-039	*N*-methyl-*N*-3-octyl-1-octylamine	255	Table 3-4	0.2	0.3	0.4	-	-
3-040	*N*, *N*-di-1-octylformamide	269	Table 3-3	82.2	70.7	41.6	18.5	14.7
3-041	*N*, *N*-di-1-octylacetamide	283	Table 3-3	-	-	1.6	1.2	1.1
3-042	tri-1-octylamine	353	Table 3-2	3.0	4.8	22.2	38.5	42.9

were each observed in less than 2%. Traces of *N*,*N*-dimethyl-1-octylamine (**3-013**) and *N*-1-octyl-*N*-3-octylformamide (**3-034**) were observed in <0.1% and 0.8%, respectively.

The first step in the reaction sequence could be the cleavage of di-1-octylamine (**3-033**) to give 1-octylamine (**3-008**). 1-Octylamine (**3-008**) thus obtained, could further react to give a similar product slate to that discussed.

Once again, formamide formation was dominant at lower temperatures. At 250 °C, 0.5 h reaction time led to *N*-methyldi-1-octylamine (**3-032**, 6.8%), *N*,*N*-di-1-octylformamide (**3-040**, 82.2%) and tri-1-octylamine (**3-042**, 3.0%) as major products. The following four compounds were identified, each in less than 1%: 1-octylamine (**3-008**), *N*,*N*-dimethyl-1-octylamine (**3-013**), *N*-1-octyl-*N*-3-octylformamide (**3-034**) and *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**). Extending the reaction time to 2 h gave *N*-methyldi-1-octylamine (**3-032**, 10.0%), *N*,*N*-di-1-octylformamide (**3-040**, 70.7%) and tri-1-octylamine (**3-042**, 4.8%) with an 88.3% conversion to products, while the 10 h reaction gave *N*-methyldi-1-octylamine (**3-032**, 9.3%), *N*,*N*-di-1-octylformamide (**3-040**, 41.6%) and tri-1-octylamine (**3-042**, 22.2%) with an 81.3% conversion to products. Again, there appears to be some equilibrium reversion to starting material. The 2 h reaction also gave a small amount of *N*-1-octyl-*N*-3-octylformamide (**3-034**, 1.2%), and trace amounts of 1-octylamine (**3-008**), 1-octanol (**3-010**), *N*,*N*-dimethyl-1-octylamine (**3-013**), *N*-1-octylformamide (**3-022**), *N*-methyl-*N*-1-octylformamide (**3-024**), *N*-methyl-*N*-1-octylacetamide (**3-029**) and *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**). Similarly, the 10 h reaction gave small amounts of *N*-1-octylformamide (**3-022**, 1.3%), *N*-methyl-1-octylformamide (**3-024**, 2.0%), *N*-1-octyl-*N*-3-octylformamide (**3-034**, 1.5%) and *N*,*N*-di-1-octylacetamide (**3-041**, 1.6%), and traces of 1-octylamine (**3-008**), 1-octanol (**3-010**), *N*,*N*-dimethyl-1-octylamine (**3-013**), *N*-methyl-*N*-1-octylacetamide (**3-029**) and *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**).

N,N-Dimethyl-1-octylamine (**3-013**) (Table 3-7). At 350 °C in HCO_2H for 10 h, *N,N*-dimethyl-1-octylamine (**3-013**) showed a 64.0% conversion. Products observed include 1-octanol (**3-010**, 14.2%), *N*-methyldi-1-octylamine (**3-032**, 22.6%), di-1-octylamine (**3-033**, 10.2%) and tri-1-octylamine (**3-042**, 4.6%). The following products were identified in lesser amounts: 2-octanone (**3-005**, 4.3%), 1-octylamine (**3-008**, 2.0%), *N*-methyl-*N*-1-octylformamide (**3-024**, 3.2%), and *N,N*-di-1-octylformamide (**3-040**, 2.0%), with *N*-methyl-1-octylacetamide (**3-029**) and *N*-1-octyl-*N*-3-octylamine (**3-031**) in traces.

At lower temperatures *N,N*-dimethyl-1-octylamine (**3-013**) was not very reactive with 49% aqueous HCO_2H. At 250 °C for 2 h, a 25.8 % conversion led to *N*-methyl-*N*-1-octylformamide (**3-024**, 10.8%) as the major product. Other products identified include *N,N*-dimethyl-2-ethyl-1-hexylamine (**3-006**, 1.8%), *N,N*-dimethyl-3-octylamine (**3-011**, 3.1%), *N*-methyldi-1-octylamine (**3-032**, 4.1%) and di-1-octylformamide (**3-049**, 2.8%). After 10 h a 19.9% conversion led to *N*-methyl-3-octylamine (**3-011**, 7.8%) and *N*-methyldi-1-octylamine (**3-032**, 7.5%), *N*-methyl-1-octylformamide (**3-024**, 3.2%), *N,N*-dimethyl-3-octylamine (**3-009**, 1.4%) and 1-octylamine (**3-008**, <0.1%).

1-Dodecylamine (**3-023**) (Table 3-8). 1-Dodecylamine (**3-023**) was very reactive in 49% aqueous formic acid. A 97.1% conversion was observed after 0.5 h. The six major products were 1-dodecanol (**3-026**, 6.1%), *N,N*-dimethyl-1-dodecylamine (**3-028**, 8.6%), *N*-1-dodecylformamide (**3-035**, 19.3%), *N*-methyl-*N*-1-dodecylformamide (**3-036**, 11.9%), *N*-methyldi-1-dodecylamine (**3-043**, 20.0%) and di-1-dodecylamine (**3-044**, 28.9%). Minor products observed were dodecane (**3-016**, 6.1%), 2-dodecene (**3-017**, 0.3%), 1-dodecanol (**3-026**, 6.1%), *N*-methyl-*N*-1-dodecylacetamide (**3-037**, 1.4%) and *N*-acetyl-*N*-1-dodecylformamide (**3-038**, 0.4%). After 10 h, a significant number of minor products were observed along with a product slate similar to the above.

Table 3-7. Products from *N*, *N*-Dimethyl-1-octylamine (**3-013**), 49% HCO_2H

Temp.(°C)				250		350
Time (h)				2	10	10
No.	Compound	MW	Identification			
3-005	2-octanone	128	Table 3-2	-	-	4.3
3-006	*N*, *N*-dimethyl-2-ethyl-1-hexylamine	157	Table 3-3	1.8	-	-
3-008	1-octylamine	129	Table 3-2	-	<0.1	2.0
3-009	*N*, *N*-dimethyl-3-octylamine	157	Table 3-3	2.0	1.4	-
3-010	1-octanol	130	Table 3-2	1.2	-	14.2
3-011	*N*-methyl-3-octylamine	143	Table 3-4	3.1	7.8	-
3-013	*N*, *N*-dimethyl-1-octylamine	157	Table 3-2	74.2	80.1	36.0
3-024	*N*-methyl-*N*-1-octylformamide	171	Table 3-4	10.8	3.2	3.2
3-029	*N*-methyl-*N*-1-octylacetamide	185	Table 3-4	-	-	0.4
3-031	*N*-1-octyl-*N*-3-octylamine	241	Table 3-4	-	-	0.5
3-032	*N*-methyldi-1-octylamine	255	Table 3-3	4.1	7.5	22.6
3-033	di-1-octylamine	241	Table 3-2	-	-	10.2
3-040	*N*, *N*-di-1-octylformamide	269	Table 3-3	2.8	-	2.0
3-042	tri-1-octylamine	353	Table 3-2	-	-	4.6

Table 3-8. Products from 1-Dodecylamine (**3-023**), 49% HC_2OH

Temp.(°C)				150		250		350
Time (h)				1	0.5	10	0.5	10
No.	Compound	MW	Identification					
3-015	1-dodecene	168	Table 3-3	-	-	-	-	1.7
3-016	dodecane	170	Table 3-2	-	-	-	0.2	2.6
3-017	2-dodecene	168	Table 3-3	-	-	-	0.3	0.6
3-019	3-dodecene	168	Table 3-3	-	-	-	-	0.3
3-023	1-dodecylamine	185	Table 3-2	41.8	11.4	0.7	2.9	9.9
3-026	1-dodecanol	186	Table 3-2	-	-	-	6.1	14.3
3-027	*N*-methyl-1-dodecylamine	199	Table 3-4	-	-	-	-	5.7
3-028	*N*, *N*-dimethyl-1-dodecylamine	213	Table 3-2	-	-	7.6	8.6	0.4
3-035	*N*-1-dodecylformamide	213	Table 3-2	57.5	81.2	47.2	19.3	9.0
3-036	*N*-methyl-*N*-1-dodecylformamide	227	Table 3-4	-	7.5	34.7	11.9	10.0
3-037	*N*-methyl-*N*-1-dodecylacetamide	241	Table 3-4	-	-	2.1	1.4	0.4
3-038	*N*-acetyl-*N*-1-dodecylformamide	255	Table 3-4	-	-	1.6	0.4	-
3-043	*N*-methyldi-1-dodecylamine	367	Table 3-4	-	-	3-03	20.0	15.1
3-044	di-1-dodecylamine	353	Table 3-3	0.7	-	2.8	28.9	30.0

The major products were 1-dodecanol (**3-026**, 14.3%), *N*-methyl-*N*-1-dodecylformamide (**3-036**, 10.0%), *N*-methyldi-1-dodecylamine (**3-043**, 15.1%) and di-1-dodecylamine (**3-044**, 30.0%). Also minor amounts of three isomers of dodecene (**3-015**, **3-017**, **3-019**) were observed.

Lower temperature runs also showed moderate to high reactivity. After 1 h, in 49% HCO_2H at 150 °C, 1-dodecylamine (**3-023**) showed 58.2% conversion to *N*-1-dodecylformamide (**3-035**, 57.5%) and a trace of di-1-dodecylamine (**3-044**, 0.7%). After 0.5 h at 250 °C an 88.6% conversion was observed with *N*-1-dodecylformamide (**3-035**, 81.2%) and *N*-methyl-*N*-1-dodecylformamide (**3-036**, 7.5%) as products. A 99.3% conversion was observed after 10 h with *N,N*-dimethyl-1-dodecylamine (**3-028**, 7.6%), *N*-1-dodecylformamide (**3-035**, 47.2%) and *N*-methyl-*N*-1-dodecylformamide (**3-036**, 34.7%) as the major products. Minor products identified were *N*-methyl-*N*-1-dodecylacetamide (**3-037**, 2.1%), *N*-acetyl-*N*-1-dodecylformamide (**3-038**, 1.6%), *N*-methyldi-1-dodecylamine (**3-043**, 3.3%) and di-1-dodecylamine (**3-044**, 2.8).

N,N-Dimethyl-1-dodecylamine (**3-028**) (Table 3-9). A 46.0% conversion was observed after reacting *N,N*-dimethyl-1-dodecylamine (**3-028**) with 49% aqueous HCO_2H for 2 h at 350 °C. The major products observed were 1-dodecanol (**3-026**, 14.8%) and *N*-methyldi-1-dodecylamine (**3-043**, 27.8%). *N*-Methyl-*N*-1-dodecylformamide (**3-036**), 1-dodecene (**3-015**) and dodecane (**3-016**) were formed in minor amounts. Extending the reaction time to 10 h led to a 57.8% conversion with a significant number of minor products - dodecane (**3-016**, 1.3%), *N*-methyl-*N*-1-dodecylacetamide (**3-037**, 0.4%) and di-1-dodecylamine (**3-044**, 4.3%). The major product was again *N*-methyldi-1-dodecylamine (**3-043**, 39.5%). Two isomeric dodecenes (**3-015**, **3-017**) were also formed in this run in minor amounts.

Table 3-9. Products from *N*, *N*-Dimethyl-1-dodecylamine (**3-028**), 49% HCO_2H

Temp.(°C)				250		350	
Time (h)				0.5	10	2	10
No.	Compound	MW	Identification				
3-015	1-dodecene	168	Table 3-3	0.4	-	1.2	2.0
3-016	dodecane	170	Table 3-3	0.2	-	0.9	1.3
3-017	2-dodecene	168	Table 3-3	0.2	-	-	0.2
3-019	3-dodecene	168	Table 3-3	0.1	-	-	-
3-026	1-dodecanol	186	Table 3-2	4.2	5.2	14.8	8.1
3-028	*N*, *N*-dimethyl-1-dodecylamine	213	Table 3-2	92.7	71.1	54.0	42.2
3-036	*N*-methyl-*N*-1-dodecylformamide	227	Tabel 4	2.2	5.8	1.3	1.9
3-037	*N*-methyl-*N*-1-dodecylacetamide	241	Table 3-4	-	-	-	0.4
3-043	*N*-methyldi-1-dodecylamine	367	Table 3-4	-	17.2	27.8	39.5
3-044	di-1-dodecylamine	353	Table 3-3	-	-	-	4.3

N,N-Dimethyl-1-dodecylamine (**3-028**) was much less reactive at 250 °C in HCO_2H for 0.5 h. Only a 7.3% conversion was observed with 1-dodecanol (**3-026,** 4.2%), and *N*-methyl-*N*-1-dodecylformamide (**3-036**, 2.2%) as the major products. Traces of 1-dodecene (**3-015**, 0.4%), dodecane (**3-016**, 0.2%), 2-dodecene (**3-017**, 0.2%) and 3-dodecene (**3-019**, 0.1%) were also identified. Extending the reaction time to 10 h showed a 28.9% conversion with 1-dodecanol (**3-026**, 5.2%), *N*-methyl-*N*-1-dodecylformamide (**3-036**, 5.8%) and *N*-methyldi-1-dodecylamine (**3-043**, 17.2%) as the only products (Table 3-9).

Since a clear mechanistic pathway (see Discussion) could not be proposed for the formation of the rearranged product **3-009**, two additional aquathermolyses were performed to see whether similar rearranged products would be formed and whether a clear mechanistic pathway could be determined. The amines of choice were *N,N*-dimethyl-1-butylamine (**3-001**) and *N,N*-dimethyl-1-hexylamine (**3-003**). These two tertiary amines were heated at 250 °C for 2 h in 49% HCO_2H since these were the conditions under which *N,N*-dimethyl-3-octylamine (**3-009**) was observed.

N,N-Dimethyl-1-butylamine (**3-001**) (Table 3-10). On heating with aqueous 49% HCO_2H at 250 °C for 2 h, *N,N*-dimethyl-1-butylamine (**3-001**) showed a 63.1% conversion (Table 3-10). The two major products were *N*-methyldi-1-butylamine (**3-004**, 32.3%) and *N*-methyl-*N*-1-butylformamide (**3-007**, 28.2%). Tri-1-butylamine (**3-014**, 1.1%) and *N,N*-di-1-butylformamide (**3-020**, 1.5%) were detected in minor amounts. There was no detection of any rearranged product, that is, no *N,N*-dimethyl-2-butylamine.

Table 3-10. Products from *N*, *N*-Dimethyl-1-butylamine (**3-001**) 49% HCO_2H

Temp.(°C)				250
Time(h)				2
No.	Compound	MW	Identification	
3-001	*N*, *N*-dimethyl-1-butylamine	101	Table 3-2	36.9
3-004	*N*-methyldi-1-butylamine	143	Table 3-4	32.3
3-007	*N*-methyl-*N*-1-butylformamide	115	Table 3-4	28.2
3-014	tri-1-butylamine	185	Table 3-3	1.1
3-020	*N*, *N*-di-1-butylformamide	157	Table 3-3	1.5

MW = molecular weight

N, *N*-Dimethyl-1-hexylamine (**3-003**) (Table 3-11). *N*, *N*-Dimethyl-1-hexylamine (**3-003**) showed a 37.5% conversion after 2 h at 250 °C in 49% aqueous HCO_2H (Table 3-11). The major product was *N*-methyl-*N*-1-hexylformamide (**3-018**, 23.9%). Other products included 1-hexanol (**3-002**, 2.8%) and *N*-methyldi-1-hexylamine (**3-021**, 10.8%). There was no detection of any rearranged products.

Table 3-11. Products from *N*, *N*-Dimethyl-1-hexylamine (**3-003**) 49% HCO_2H

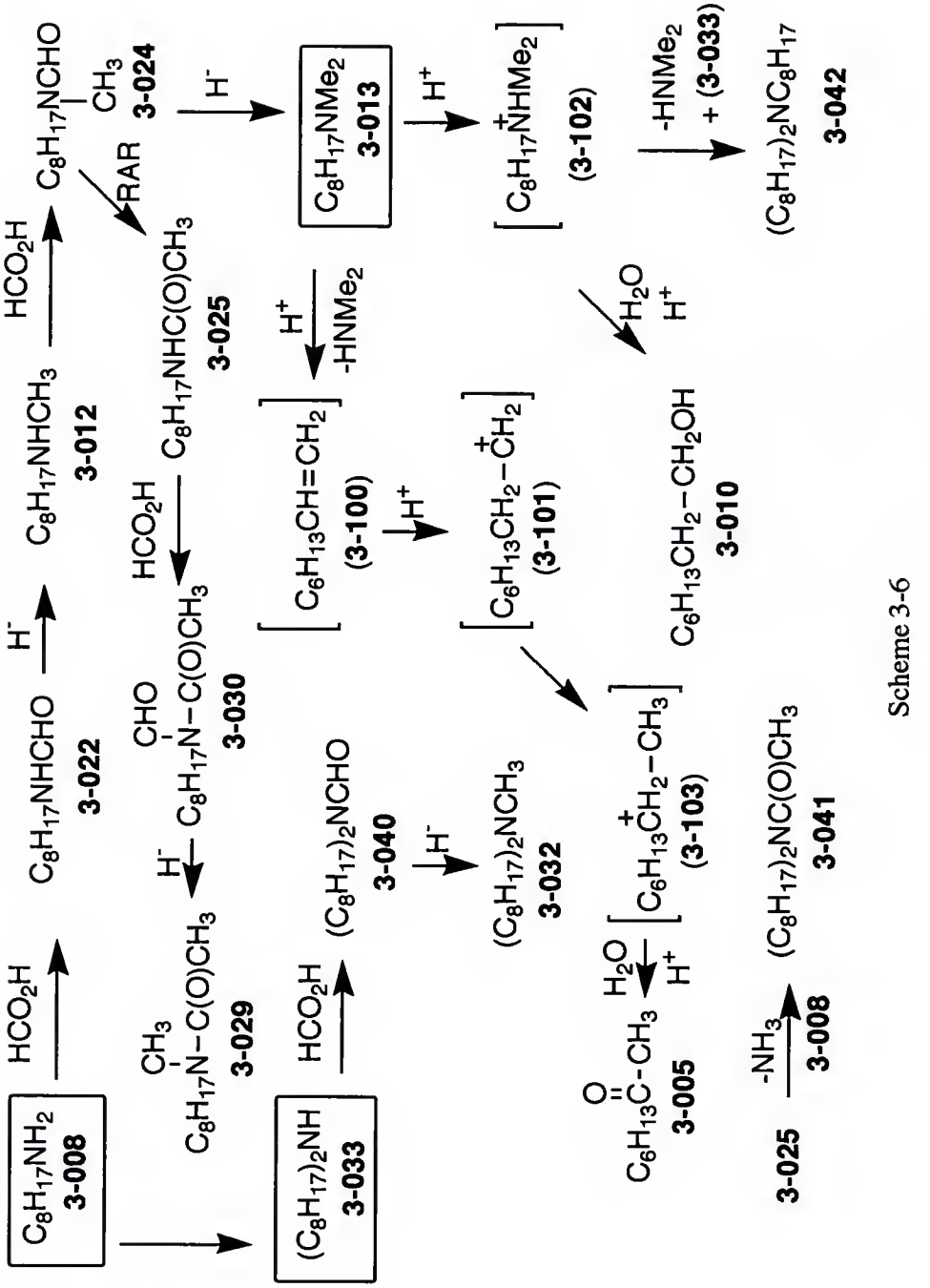
Temp.(°C)				250
Time(h)				2
No.	Compound	MW	Identification	
3-002	1-hexanol	102	Table 3-3	2.8
3-003	*N*, *N*-dimethyl-1-hexylamine	129	Table 3-2	62.5
3-018	*N*-methyl-*N*-1-hexylformamide	143	Table 3-4	23.9
3-021	*N*-methyldi-1-hexylamine	199	Table 3-4	10.8

MW = molecular weight

General Discussion

The aliphatic primary amines showed the dominant reaction pathway as *N*-formylation with subsequent reduction to give *N*-methyl and *N*,*N*-dimethylalkylamines. That is, under the above mentioned aquathermolysis conditions the aliphatic amines are involved in conventional reactions where the formic acid is behaving as a hydride donor and as a formylating agent. In the case of 1-dodecylamine (**3-023**), in addition to the above mentioned pathway, elimination of NH_3 and $HNMe_2$ to the corresponding alkene was also observed; which could then undergo isomerization. The secondary amine, di-1-octylamine (**3-033**) underwent conventional *N*-formylation and subsequent reduction to the *N*-methyl derivative. Also, formation of the mono- and tri-1-octyl derivatives is representative of a cleavage process. The tertiary amines underwent reductive cleavages to primary and secondary amines, which subsequently followed the reaction sequences seen for the primary amines.

Formation of *N*-1-octylformamide (**3-022**) and subsequent reduction products was the major reaction pathway for 1-octylamine (**3-008**) (Scheme 3-6). It is evident that at lower temperatures there is significant formamide product formation as well. Subsequent reduction of the *N*-formylation product is supported by the presence of *N*-methyl-1-octyamine (**3-012**) and *N*,*N*-dimethyl-1-octylamine (**3-013**). Amine **3-012**, the reduced product of formamide **3-022** underwent a second formylation to give *N*-methyl-*N*-1-octylformamide (**3-024**). Subsequent reduction of amide **3-024** leads to *N*,*N*-dimethyl-1-octylamine (**3-013**). Tri-1-octylamine (**3-042**) can be formed by the reaction of amine **3-013** with di-1-octylamine (**3-033**). In this process, amine **3-013** undergoes loss of N,N-dimethylamine. Di-1-octylamine (**3-033**) is the product of self condensation of 1-octylamine **3-008**. Conventional formylation of amine **3-033** generates *N*,*N*-di-1-octylformamide (**3-040**) which can be further reduced to the *N*-methyl derivative **3-032**. The formation of 1-octanol (**3-010**) suggests the presence of 1-octene.



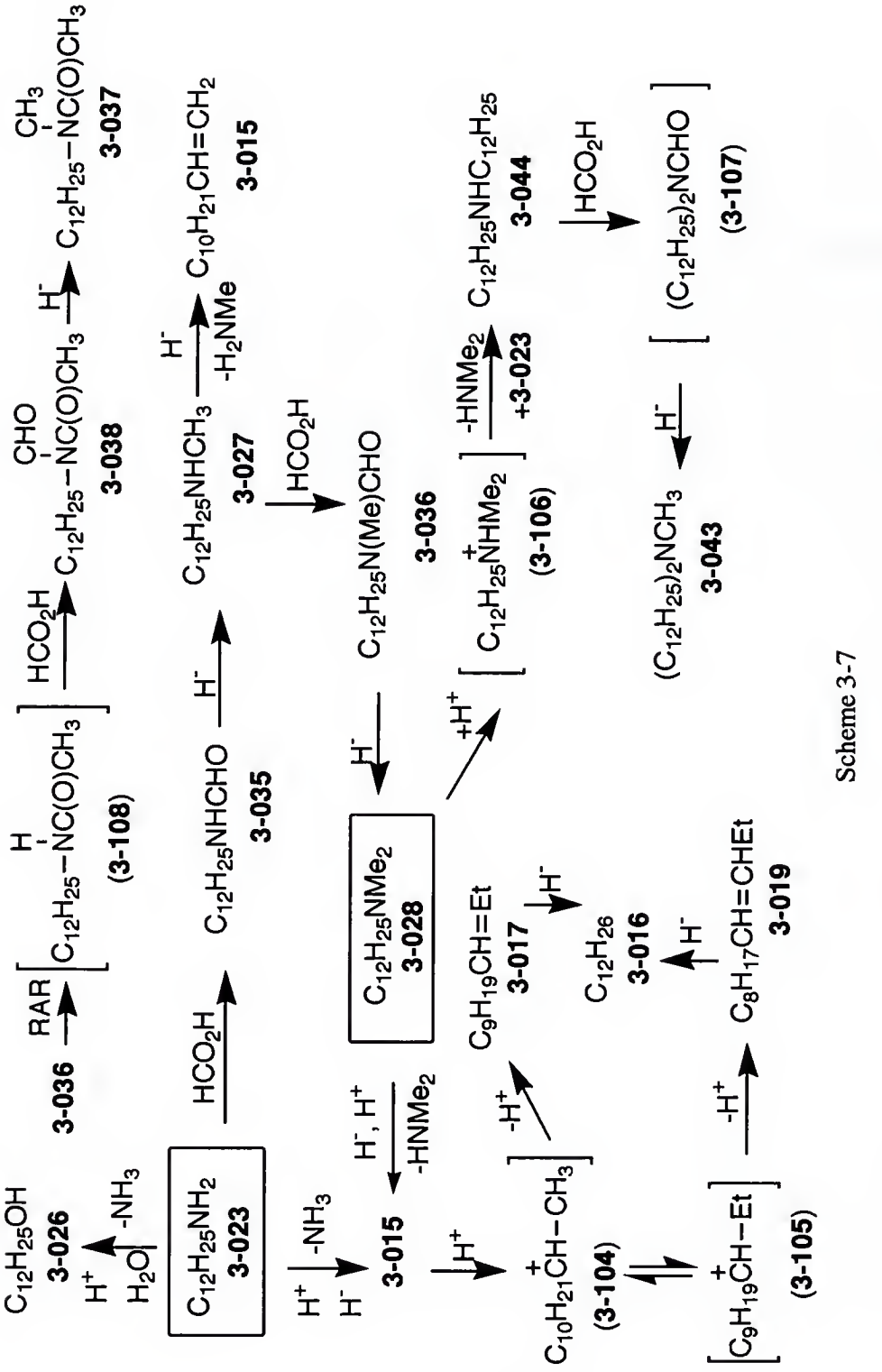
Scheme 3-6

N-1-Octylacetamide (**3-025**) may have been produced under aquathermolysis conditions *via* a rearrangement of *N*-methyl-*N*-1-octylformamide (**3-024**) (Scheme 3-6), although we have been unable to find an example of an acid promoted rearrangement of a formamide to an acetamide. The other acetyl derivatives would have been formed from further reaction of **3-025**. *N*-Acetyl-*N*-1-octylformamide (**3-030**) is produced from the *N*-formylation of acetamide **3-025**. Subsequently, reduction of amide **3-030** would generate *N*-methyl-*N*-1-octylacetamide (**3-029**) (Scheme 3-6).

Similarly, the other primary amine, 1-dodecylamine (**3-023**) gave *N*-1-dodecylformamide (**3-035**) as the main product under all reaction conditions, the subsequent reduction was supported by formation of the various *N*-methyl derivatives. In contrast to implied formation of 1-octene, formation of 1-dodecene is observed as well as the 2- and 3- isomer (Scheme 3-7).

Under aquathermolysis conditions 1-dodecylamine (**3-023**) underwent conventional *N*-formylation to give *N*-1-dodecylformamide (**3-035**) (Scheme 3-7). Subsequent reduction of amide **3-035** generates the *N*-methyl derivative **3-027**. Loss of methylamine from **3-027** results in the formation of 1-dodecene (**3-015**). Alternately, alkene **3-015** may be generated either by the loss of ammonia from 1-dodecylamine (**3-023**) or by the loss of *N*,*N*-dimethylamine from *N*,*N*-dimethyl-1-dodecylamine (**3-028**). In turn, the amine **3-028** is generated from the reduction of *N*-methyl-*N*-1-octylformamide (**3-036**) which is produced by the *N*-formylation of *N*-methyl-1-dodecylamine (**3-027**).

1-Dodecene can undergo isomerization to both the 2- (**3-017**) and the 3- (**3-019**) derivative (Scheme 3-7). Reduction of either of these alkenes would lead to dodecane (**3-016**). In addition, loss of ammonia from 1-dodecylamine (**3-023**) and a formic acid catalyzed reaction with water generated 1-dodecanol (**3-026**). *N*,*N*-Dimethyl-1-dodecylamine (**3-028**), through loss of *N*,*N*-dimethylamine and subsequent condensation with amine **3-023**, was converted to di-1-dodecylamine (**3-044**). Formylation of amine **3-044** leads to *N*-methyldi-1-dodecylamine (**3-043**).



Scheme 3-7

The acetyl derivatives may be justified *via* the amide **3-036**, though the corresponding *N*-1-dodecylacetamide (**3-108**) was not detected by the GC/MS analysis (Scheme 3-7). *N*-Acetyl-*N*-1-dodecylformamide (**3-038**) may be explained *via* the formylation of **3-108**, with subsequent reduction leading to *N*-methyl-*N*-1-dodecylacetamide (**3-037**). Again, there is no literature precedence for the formation of acetamide **3-108** from the formamide **3-036**.

As expected di-1-octylamine (**3-033**) underwent *N*-formylation. If a simple reduction were the only possible reaction pathway, then *N*-methyldi-1-octylamine (**3-032**) would be the only next logical product. However, it is apparent that reductive cleavage takes place (on the starting amine), due to the presence in the product slate of similar products to those obtained from 1-octylamine (**3-008**) (Scheme 3-6). Formation of *N*-1-octyl-*N*-3-octylformamide (**3-034**) and *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**) appear to be from the isomerization of the octyl moiety before the formylation and reduction take place (Table 3-9).

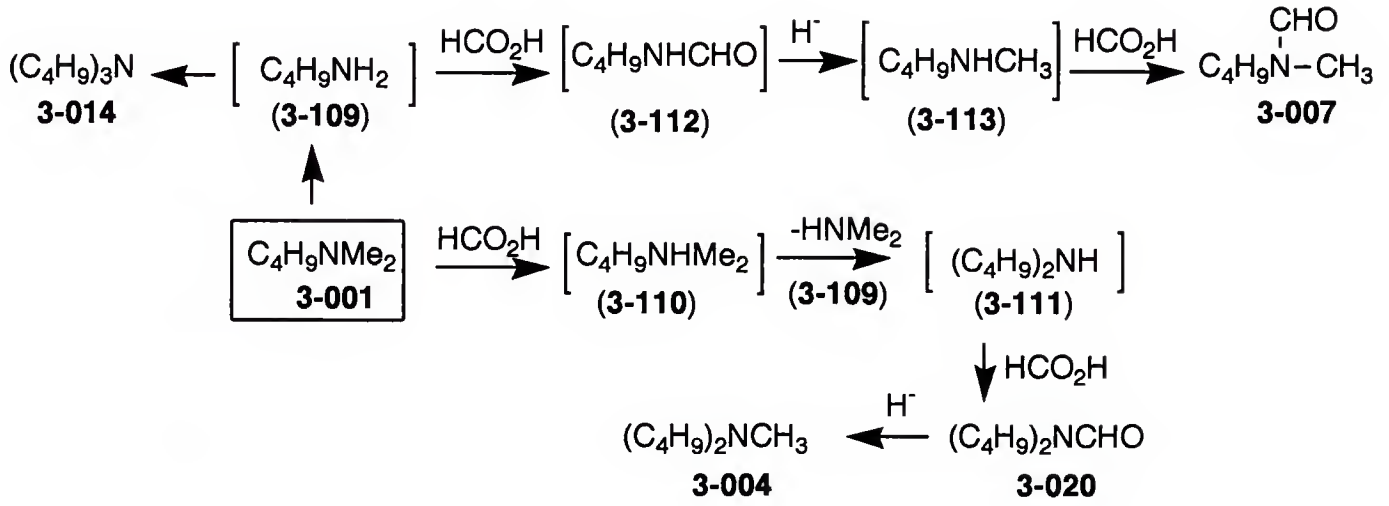
Since the tertiary amine could not undergo *N*-formylation directly, *N*-formyl and subsequent reduction products would have to be formed after reductive cleavage of the starting amine. Reductive cleavage explains formation of the alcohol and *N*-methyldialkylamine major products from both *N,N*-dimethyl-1-octylamine (**3-013**) (Scheme 3-6) and *N, N*-dimethyl-1-dodecylamine (**3-028**) (Scheme 3-7).

N,N-Dimethyl-1-octylamine (**3-013**) may be reductively cleaved to amine **3-008** and/or amine **3-012**, which can each undergo the reaction pathways outlined in Scheme 3-6. As shown in Chapter II, formic acid may act both as a reducing and as an oxidizing agent. Its role as an oxidizer may explain the formation of octanone (**3-005**). Again the rearranged derivatives **3-006**, **3-009**, **3-011** and **3-031** (Table 3-7) may be from the isomerization of the octyl moiety.

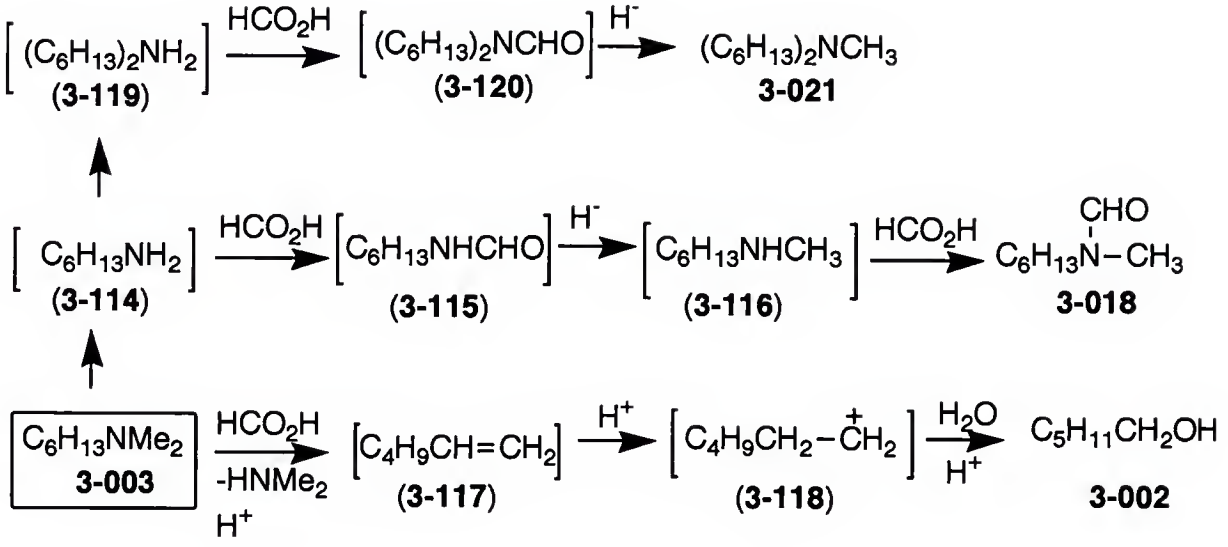
N,N-Dimethyl-1-butylamine (**3-001**) underwent conventional formylation and subsequent reduction to generate its products (Scheme 3-8). As stated previously, this

tertiary amine **3-001** would undergo reductive cleavage to the primary amine before formylation took place. However, the corresponding primary amine, 1-butylamine (**3-109**) was not detected by GC/MS. Still, *N*-methyl-*N*-1-butylformamide (**3-007**) does support the above pathway, since its (**3-007**) formation may be viewed through the formylation of **3-109**, to form **3-112**, which would subsequently be reduced to **3-113** and finally, formylated once again to give amide **3-007**. Likewise, *N*,*N*-di-1-butylformamide (**3-020**) is formed *via* formylation of **3-111**. The intermediate **3-111** is generated from condensation of **3-110** and **3-109** accompanied by the loss of *N*,*N*-dimethylamine. Tri-1-butylamine (**3-014**) is a self condensation product *via* intermediate **3-109**. Simple reduction of **3-020** leads to *N*-methyldi-1-butylamine (**3-004**) (Scheme 3-8).

The products from *N*,*N*-dimethyl-1-hexylamine (**3-003**) are formed similarly to those of amine **3-001** (Scheme 3-9). As seen with amine **3-001**, formation of *N*-methyl-*N*-1-hexylformamide suggests the presence of intermediates **3-114**, **3-115** and **3-116**, though they were not detected by the GC/MS analysis. *N*-Formylation of intermediate **3-114** would give **3-115**, which could undergo reduction to **3-116**. Subsequent reduction of intermediate **3-116** would generate formamide **3-018**. Since these intermediates were not detected (**3-114**--**3-116**), this may suggest that they are being consumed within the reactions. *N*-Methydi-1-hexylamine (**3-021**) may be explained similarly, *via* formylation and reduction of **3-119** and **3-120**, respectively. As with 1-octylamine (**3-008**), formation of 1-hexanol (**3-002**) implies the presence of an alkene - 1-hexene (**3-117**) (Scheme 3-9).


(C4H9)3N
3-014
C4H9NH2
(3-109)
HCO2H
C4H9NHCHO
(3-112)
H-
C4H9NHCH3
(3-113)
HCO2H
CHO
C4H9N–CH3
3-007
C4H9NMe2
3-001
HCO2H
C4H9NHMe2
(3-110)
-HNMe2
(3-109)
(C4H9)2NH
(3-111)
HCO2H
H-
(C4H9)2NCH3
3-004
(C4H9)2NCHO
3-020

Scheme 3-8


[(C6H13)2NH2]
(3-119)
HCO2H
[(C6H13)2NCHO]
(3-120)
H-
(C6H13)2NCH3
3-021
[C6H13NH2]
(3-114)
HCO2H
[C6H13NHCHO]
(3-115)
H-
[C6H13NHCH3]
(3-116)
HCO2H
CHO
C6H13N–CH3
3-018
C6H13NMe2
3-003
HCO2H
-HNMe2
H+
[C4H9CH=CH2]
(3-117)
H+
[C4H9CH2–CH2]+
(3-118)
H2O
H+
C5H11CH2OH
3-002

Scheme 3-9

Conclusions

The general trend observed from the results obtained is that *N*-formylation is the dominant reaction pathway. Under the above mentioned aquathermolysis conditions the aliphatic amines were involved in conventional reactions where the formic acid behaved both as a hydride donor and as a formylating agent. The aliphatic primary amines showed the dominant reaction pathway as *N*-formylation with subsequent reduction to give *N*-methyl and *N*, *N*-dimethylalkylamines. In addition to the above mentioned pathway, there was also elimination of simple amines to yield the corresponding alkene which could further undergo isomerization. The secondary amine also underwent conventional *N*-formylation and subsequent reduction to the *N*-methyl derivative, with formation of the mono- and tri-1-octyl derivatives is representative of a reductive cleavage process. The tertiary amines underwent reductive cleavages to primary and secondary amines, which subsequently followed the reaction sequences seen for the primary amines.

1-Octylamine (**3-008**) displayed significant amounts of *N*-formylation and subsequent reduction products. This trend was observed at 350 °C as well as at lower temperatures. There was also some self condensation products - di-1-octylamine (**3-033**) and tri-1-octylamine (**3-042**).

Synthesis of authentic *N*-1-octylacetamide (**3-025**) and investigation of its MS pattern suggest that it could be a plausible product under the aquathermolysis conditions. However, since the suggested pathway for its formation lacks literature precedence and is an anomaly, amide **3-025** may be alternately explained as an obscure impurity.

1-Dodecylamine (**3-023**) also gave significant *N*-formylation. In addition, formation of alkenes was observed *via* the loss of ammonia and *N*, *N*-dimethylamine. These alkenes were subject to isomerization. The 2- and 3-dodecylamine were not observed as products in the aquathermolysis reactions. Thus, it can be concluded that the hypothesis of amination of the alkenes to the corresponding amines is unfounded.

Di-1-octylamine (**3-033**), also gave *N*-formylation, but it was not significant. This secondary amine also underwent reductive cleavage and subsequent reduction, with products similar to those from 1-octylamine (**3-008**).

Both tertiary amines (**3-013**, **3-028**) were, as expected, less reactive than the primary and secondary amines. Most products were generated from a primary or secondary amine, which was produced by reductive cleavage of the corresponding tertiary amine.

A number of rearranged products were identified, but may well be inadvertent impurities. Though, MS investigations indicate *N*,*N*-dimethyl-3-octylamine (**3-009**) as a possible product, aquathermolysis of *N*,*N*-dimethyl-1-butylamine (**3-001**) and *N*,*N*-dimethyl-1-hexylamine (**3-003**) revealed no rearranged products similar to amine **3-009** and therefore could shed no light on a possible rearrangement pathway. It is very likely that the rearranged amine **3-009** might have been an impurity. It appears that rearrangement is not a normal pathway under the reaction conditions.

Experimental

^{1}H NMR spectra were recorded either on a Gemini 300 (300 MHz) Varian VXR 300 (300 MHz) or a General Electric QE (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) used as an internal standard. Coupling constants (*J* values) are reported in hertz (Hz). Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F_{254} plastic plates (0.2 mm thick) using iodine as an indicator to visualize the product compounds.

General procedure for the synthesis of *N, N*-dimethyloctylamines

N, N-Dimethyl-3-octylamine (**3-009**). 3-Octylamine (1 eq., 2.4 g, 18.8 mmol), formaldehyde (4 eq., 2.3 g, 75.0 mmol) and titanium tetraisopropoxide (2 eq. 10.4 g, 37.5 mmol) was refluxed in diglyme (5.0 ml) at 70 °C. After 2 h the reaction was cooled to room temperature and sodium borohydride (1.5 eq, 1.1 g, 28.1 mmol) was added. The reaction was then stirred at room temperature (7 h). After cooling to room temperature, the reaction was diluted with Et_2O (25 mL) and aqueous ammonium hydroxide was added to precipitate the inorganic product, which was filtered and washed with excess Et_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Dyglime was removed by distillation *in vacuo*. A pale colored oil (1.6 g, 57%) was isolated. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 6.5) ($\underline{CH_3}CH_2$), 1.0 (t, 3H, J = 7.0) ($\underline{CH_3}CH_2CH$), 1.2 (s, 8H) ($4CH_2$), 1.4 (m, 2H) ($CH_3\underline{CH_2}CH$), 2.3 (s, 6H) (NMe_2), 2.6 (m, 1H) (CH). ^{13}C NMR ($CDCl_3$): δ 9.5, 13.9, 22.8, 25.1, 27.0, 31.5, 32.8, 35.0, 58.9. LR MS M^+ = *m/z* 157 ($C_{10}H_{23}N$); base peak = *m/z* 86 ($C_5H_{12}N$).

N, N-Dimethyl-2-octylamine (**3-045**). This product was obtained as an off-white oil which solidified upon cooling. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 7.0) ($\underline{CH_3}CH_2$), 1.1 (d, 3H, J = 6.7) ($\underline{CH_3}CH$), 1.3 (s, 8H) ($4CH_2$), 1.7 (m, 2H) ($\underline{CH_2}CH$), 2.2 (S, 6H) (NMe_2), 2.9 (m, 1H) (CH). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.6, 23.5, 26.0, 29.4, 29.6, 31.8, 39.5, 54.9. LR MS M^+ = *m/z* 157 ($C_{10}H_{23}N$); base peak = *m/z* 72 ($C_4H_{10}N$).

N-1-Octylacetamide (**3-025**). 1-Octylamine (1ml) was dissolved in acetic anhydride (2.7 mL) and warmed for about 0.5 h. The mixture was then cooled to room temperature and diluted with ether, washed with 1M HCl and then 10% NaOH. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. A pale yellow oil (680 mg, 68%) was isolated. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 6.7), 1.3 (m, 10H), 1.5 (t, 2H,

J = 7.4), 2.0 (s, 3H), 3.2 (q, 2H, J = 6.7), 6.3 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.5, 23.1, 26.8, 29.1, 29.2, 29.4, 31.7, 39.6, 170.2. LR MS M^+ = m/z 171 ($C_{10}H_{21}NO$); base peak = m/z 30 (CH_4N).

N-1-Dodecylformamide (**3-035**). 1-Dodecylamine (10.0 g, 54 mmol) was suspended in an excess of aqueous formic acid (88%) (2.48 g, 108 mmol). The mixture was refluxed in benzene (150 mL) under Dean-Stark conditions for the azeotropic removal of water. The reaction was refluxed for 18 h; cooled to room temperature and the solvent removed *in vacuo*. The pale yellow solid was recrystallized from petroleum ether to give the title compound as white flakes (9.70 g, 84%) (m.p. 33.5-35 °C) (Lit. [59MI388] m.p. 35-36 °C); ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 7.0), 1.3 (s, 18H), 1.5 (t, 2H, J = 7.0), 3.2 (q, 2H, J = 7.0), 5.7 (br. s, 1H), 8.2 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 26.8, 29.2, 29.3, 29.5, 29.5 (2C), 29.6, 29.7, 31.8, 38.2, 161.1. HR MS m/z 213.2090 (M^+, 18%, $C_{13}H_{27}NO$ requires 213.2090).

General procedure for the synthesis of primary amines

3-Octylamine (**3-046**). Sodium cyanoborohydride (7.0 eq, 17.8 g, 273.5 mmol) was suspended in absolute EtOH (100 mL) and 3-octanone (1.0 eq, 5.0 g, 39.1 mmol) in absolute EtOH (50 ml) was added dropwise *via* addition funnel. Ammonium acetate (10.0 eq, 30.1 g, 390.1 mmol) was then added and the mixture was allowed to reflux at 70 °C. After 5 h the reaction mixture was cooled to room temperature, acidified with conc. HCl - to pH 2; then basified with 20% NaOH. The aqueous layer was then extracted with $CHCl_3$ (100ml, 3X); dried over Na_2SO_4 and concentrated to give a pale yellow viscous oil (3.1 g, 62%). The sample was used in subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 7.0) ($\underline{CH_3}CH_2$), 1.0 (t, 3H, J = 6.9) ($\underline{CH_3}CH_2CH$), 1.3 (br. s, 8H) ($4CH_2$), 1.7 (m, 2H) ($CH_3\underline{CH_2}CH$), 3.0 (q, 1H, J = 7.0) (CH), 7.2 (d,

2H) (NH_2). ^{13}C NMR ($CDCl_3$): δ 9.5, 13.9, 22.8, 25.1, 27.0, 31.5, 32.8, 35.0, 58.9. LR MS M^+ = *m/z* 129 ($C_8H_{19}N$), base peak = *m/z* 58 (C_3H_2N).

2-Dodecylamine (**3-049**). This compound was obtained crude as a pale yellow viscous oil by the procedure outline above for **3-046**. The sample was then purified by Kugelrohr distillation to produce a colorless oil (2.0 g, 66%). ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, *J* = 6.3) ($\underline{CH_3}CH_2$), 1.0 (t, 3H, *J* = 6.9) ($\underline{CH_3}CH_2$), 1.1 (d of d, 3H, *J* = 6.4, 6.3) ($\underline{CH_3}CH$), 1.3 (s, 16H) ($8CH_2$), 1.7 (s, 2H) (CH), 2.3 (d, 1H, *J* = 7.0) (CH). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.5, 23.7, 26.3, 29.2, 29,5 (2C), 29.6, 31.8, 40.0, 46.8. HR MS *m/z* 185.2167 (M^+, 0.5%, $C_{12}H_{27}NO$ requires 185.2167).

3-Dodecylamine (**3-050**). This compound was obtained crude as a pale yellow viscous oil by the procedure outline above for **3-046**. The sample was then purified by Kugelrohr distillation to produce a colorless oil (07 g, 68%). ^1H NMR ($CDCl_3$): δ 0.9 (m, 6H) ($N\underline{CH_3}CH_2$; $\underline{CH_3}CH_2$), 1.0 (t, 3H, *J* = 6.9) ($\underline{CH_3}CH_2$), 1.3 (s, 16H) ($8CH_2$), 1.4 (m, 2H) ($CH\underline{CH_2}$), 1.5 (m, 2H) (NH_2), 2.6 (m, 1H) (CH). ^{13}C NMR ($CDCl_3$): δ 10.3, 14.0, 22.6, 23.7, 26.2, 29.2, 29,5, 29.6, 29.8, 30.6, 31.8, 37.5, 52.6. HR MS *m/z* 185.2158 (M^+, 0.5%, $C_{12}H_{27}NO$ requires 185.2158).

Aquathermolysis: General.[3.7]

The purities of all starting materials were checked by GC prior to use. 49% Aqueous formic acid was deoxygenated with argon for 1 h prior to use. The model compound (1 g) and the acid (7 mL) were charged into a nitrogen blanketed stainless steel bomb which was then sealed. The reactor was then kept without agitation in a fluidized sand bath (model SBS-4) set at 350 ± 5 °C (150 and 250 °C when appropriate). After the reaction period, the reactor was immediately quenched in a stream of cold air and then dry

3.7 All aquathermolysis runs were performed by Elena S. Ignatchenko at the University of Florida.

ice. The reaction mixture was then worked up as previously described [90EF493], and subjected to GC analyses on a Hewlett Packard 5890 instrument (flame ionization detector, FID) fitted with a 15 m capillary column (SPB-1) and an oven temperature program of 10 °C/min from 50 - 250 °C. Gas chromatographic/mass spectral analyses were obtained on a Hewlett Packard 5890 Series II Gas Chromatograph with a HP 5972A Mass Selective Detector (MSD).

Product identification. Within the reaction mixtures, the identities of all the starting materials, and some of the products [**3-005**, **3-006**, **3-008**, **3-009**, **3-010**, **3-012--3-024**, **3-026**, **3-027**, **3-028**, **3-032**, **3-033**, **3-035**, **3-040--3-042** and **3-044**] were confirmed by comparison of their retention times and mass spectral fragmentation patterns with those of the authentic compounds, commercially available or prepared independently. Table 3-2 records the source and mass spectral fragmentation patterns of the authentic compounds used, either as starting materials or for the identification of products. For some other products [**3-006**, **3-009**, **3-012**, **3-015**, **3-017--3-022**, **3-026**, **3-032**, **3-040**, **3-041** and **3-044** for which authentic samples were not available, identification was by comparison of their mass spectral (MS) fragmentation patterns with published mass spectra (Table 3-3). The structure for the remaining products (Table 3-4) [**3-011**, **3-024**, **3-025**, **3-027**, **3-029--3-031**, **3-034**, **3-036--3-039** and **3-043**] were assigned by consideration of their mass spectral fragmentation patterns together with the starting materials, reaction conditions and reasonable mechanistic pathways for their formation from the starting materials. Tables 3-3 and 3-4 record the mass spectral fragmentation pattern of those compounds for which authentic samples were not available; the structural assignments of these were based either on the fragmentation pattern of that same compound reported in the literature (Table 3-3), or deduced from the fragmentation observed and reported in detail in the appendix (Table 3-4, Section 3.6).

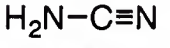
CHAPTER IV
BENZOTRIAZOLE-1-CARBOXAMIDINIUM TOSYLATE: AN ALTERNATIVE METHOD FOR THE CONVERSION OF AMINES TO GUANIDINES

Introduction

Much research has been directed toward the synthesis of guanidines as many biologically active compounds contain guanidine moieties. Established methods for the preparation of guanidines include the use of cyanamide [04CB1681, 50CB1260, 27OS46, 46HCA324, 50JOC884, 50JOC890, 51CJC718, 51JCS1252, 71JA5542], S-alkylthiouronium salts and derivatives [43OS345, 55OS440, 58CJC1541, 62RTC69, 63JMC275, 74JOC1166, 87JOC1700, 89SC1787, 90JCS(P1)311, 91MI425, 92MI119, 92TL5933, 93TL7677, 94SC321, 94TL977], aminoiminosulfonic acids [86JOC1882, 87S777, 88TL3183, 90SC3433], 3,5-dimethylpyrazole-1-carboxamidine nitrate [58CJC1541, 90JCS(P1)311, 91MI425, 94SC321], pyrazole-1-carboxamidine hydrochloride [92JOC2479, 93SC3055, 93TL3389] and *N,N'-bis*(tert-butyloxycarbonyl)- and *N,N'-bis*(benzyloxycarbonyl)thiourea [94TL977].

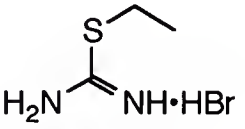
Historically, preparation of guanidines has been accomplished using cyanamide (**4-001**) [04CB1681, 46HCA324, 4270S46, 50CB1260, 50JOC884, 50JOC890, 50CJC718, 51JCS1252, 71JA5542]. The cyanamide methodology has usually been used to synthesize aromatic guanidines such as phenylguanidine, dibenzoylphenylguanidine and *p*-methylphenylguanidine nitrate [04CB1681]. Guanidines substituted with electron-withdrawing groups have also been synthesized this way and include *m*- and

p-nitrophenylguanidine, α,α-diphenylguanidine, phenylbenzoylguanidine and *m*- and *p*--nitrophenylbenzoylguanidine [50CB1260]. Reaction yields of this cyanamide process have been moderate to good (50--80%) - but the reaction conditions have often been harsh involving refluxing at high temperatures for long periods of time [50JOC884, 50JOC890, 51CJC718]. Even more harsh conditions involve fusion at 200 - 260 °C [51JCS1252]. These conditions were used to prepare aliphatic guanidines in moderate yields. Compound **4-001** has also been used to prepare guanidines from amino acids--but long reaction times (several days) are required [71JA5542] with the products isolated as picrates.

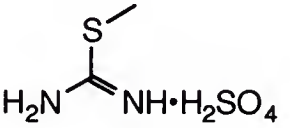


4-001

S-Alkylthiouronium halides or salts have been used effectively to synthesize guanidines [58CJC1541, 63JMC275, 71JA5542, 92TL5933]. More specifically, S-ethylthiourea hydrogen bromide (**4-002**) (which requires synthesis from thiourea) [55OS440] has been used to convert glycine to guanidinoacetic acid in 80 - 90% yield. S-Methylthiourea sulfate/hydrogen sulfate (**4-003**) [43OS345, 62RTC69, 74JOC1166, 90JCS(P1)311, 92MI119, 94SC321] has been used to generate a variety of compounds. Compound **4-003** has been used in the synthesis of dicyanodiamide [43OS345] and to generate monosubstituted guanidines [90JCS(P1)311] (reaction time 48 h).



4-002

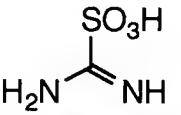


4-003

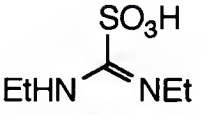
Conversion of amines to guanidines is often carried out with these alkylthiouronium salts (**4-002**, **4-003**) under basic conditions [74JOC1166, 92MI119], but products can be difficult to purify due to the presence of the highly polar, basic

guanidino group. Guanylation of the aminomethyl derivatives of azepines [94SC321] has also been accomplished using this methodology.

Aminoiminomethanesulfonic acid (**4-004**) and its phenyl derivatives [86S777, 86JOC1882, 88TL3183] have been used to generate guanidines at ambient temperature within a matter of minutes. Products precipitate from the reaction mixture and can be purified by crystallization. Formamidinesulfinic acid which is used to generate the aminoiminosulfinic acids may be used as a guanylating reagent [88TL3183]. The sulfonic acid derivatives are crystalline and are stable over a few weeks. Displacement of the HSO_3^- groups takes place more easily than the alkylmercaptan anion of the S-alkylthioureas in classical synthetic procedures [88TL3183]. Ethylaminoethyliminomethanesulfonic acid (**4-005**) has been used in the amidination of lysine [90SC3433] of which the amidination is known to occur regiospecifically.

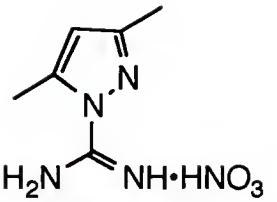


4-004

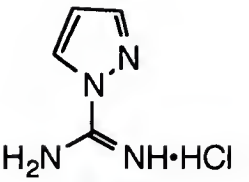


4-005

Literature searches thus far have revealed two pyrazole reagents for the conversion of amines to guanidines: i) 3,5-dimethylpyrazole-1-carboxamidine nitrate (**4-006**) [63JA275, 86S777, 90JCS(P1)311, 91MI425, 94SC321] and ii) pyrazole-1-carboxamidine hydrochloride (**4-007**). Both reagents have been used effectively with amines and are improvements over the existing methods. However, **4-006** requires a strongly basic medium and/or heat when used in the formation of guanidines [86S777].



4-006

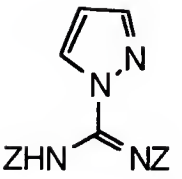


4-007

Compound **4-006** is a convenient reagent for the synthesis of monosubstituted guanidines [90JCS(P1)311]. Reactions are normally carried out at 40 °C (about 4 h) or room temperature (2 days) depending on the substrate. This guanylnitrate reagent has also been used in the synthesis of analogs of the antihypersensitive agent guanetidine [94SC321], but with low isolated yields. Products were isolated as nitrates.

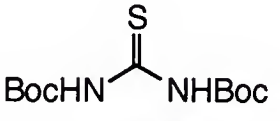
A more versatile reagent is pyrazole-1-carboxamidine hydrochloride (**4-007**) [92JOC2497, 93SC3055, 93TL3389]. Pyrazole **4-007** reacts with primary and secondary amines to produce guanidine hydrochlorides in good yields, and is also a useful reagent for peptide synthesis when standard methods for the conversion of amines to guanidines are not practical [92JOC2497]. The gaunylpryazole **4-007** can be stored in aqueous solution for short periods of time and is used in stoichiometric amounts at room temperature. The pyrazole by-product is soluble in ether and can be easily removed [92JOC2497]. This is a welcomed advantage over **4-006** which requires refluxing and two equivalents of the amine.

Protection of **4-007** [93SC3055, 93TL3389] is known to enhance its reactivity. *N,N-bis-*(*tert*-Butyloxycarbonyl)-1-carboxamidinepyrazole (**4-008a**) and *N,N'-bis-*(benzyloxycarbonyl)-1-carboxamidinepyrazole (**4-008b**) have been used for mild and efficient preparation of monosubstituted guanidines [93TL3389] and in peptide synthesis [93SC3055]. The bis-urethane protected (Boc, Cbz) derivatives **4-008a** and **4-008b** were found to be more reactive reagents for the conversion of amines to guanidines than the guanyl hydrochloride **4-007** [93TL3389].

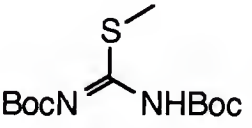


4-008a: Z = Boc
4-008b: Z = Cbz

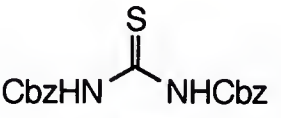
Slight modification of the guanyl reagent allows for the generation of (protected) guanidines which are more soluble in organic solvents. Acyl- [92TL5933] and cyanothioureas [89TL7313] have been used for the preparation of monosubstituted guanidines. Normally, this occurs as a one pot, two stage procedure. Also, bis-protection of the guanidine reagent with *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) enhances reactivity. *N,N-bis*(*tert*-Butoxycarbonyl)thiourea (**4-009**) or S-methylisothiourea (**4-010**) [87JOC1700, 92MI119, 93TL7677, 94TL977] and *N,N'-bis*(benzyloxycarbonyl)thiourea (**4-011**) [87JOC1700, 92MI119, 94TL977] have been used to synthesize protected guanidines which are easy to purify.



4-009



4-010

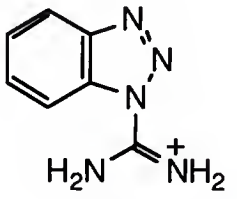


4-011

Kozikowski and co-workers have used these protected guanidine reagents (**4-009--4-011**) [94TL977] to synthesize guanidines in excellent yields starting from alcohols, while Kim and co-workers have enhanced the reactivity of highly deactivated amines and the bis-Boc protected guanidines by treatment with $HgCl_2$ or $CuCl_2$ [93TL7677].

The usefulness of benzotriazole (**4-012**) as a synthetic auxiliary is well documented [91T2683]. Benzotriazole (**4-012**) displays two extremely important properties due to its moderate acidity (pK_a 8.2): (i) it easily undergoes Mannich-type condensation with an aldehyde and a compound with an active hydrogen to form a variety

of benzotriazole adducts, and (ii) it's anion is an especially good leaving group which can be displaced by various types of nucleophiles. In extending this latter property we now report a novel, effective and convenient reagent for the mild and efficient conversion of amines to guanidines utilizing benzotriazole methodology. Our approach utilizes benzotriazole-1-carboxamidinium tosylate (**4-013**) to generate substituted guanidines from amines.



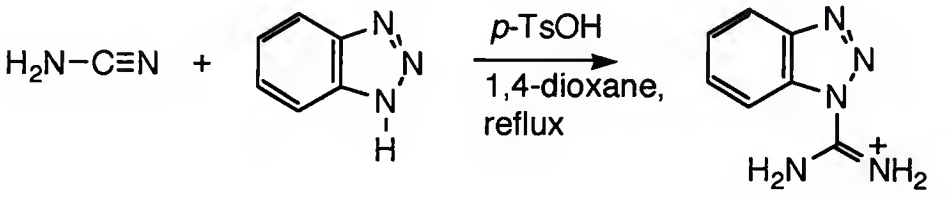
4-013

Results and Discussion

Benzotriazole-1-carboxamidinium tosylate (**4-013**) was conveniently prepared in good yield by modification of a procedure previously reported for the preparation of pyrazole-1-carboxamidine hydrochloride (**4-007**) [92JOC2497]: molar equivalents of benzotriazole, cyanamide and *p*-toluenesulfonic acid (*p*-TsOH) were refluxed in 1,4-dioxane (Scheme 4-1). The amidinium tosylate **4-013** preciptated from the reaction during reflux, and could be filtered from the reaction mixture. Recrystallization gave pure benzotriazole-1-carboxamidinium tosylate (**4-013**) (77%) as stable, non-hygroscopic, fine white needles.

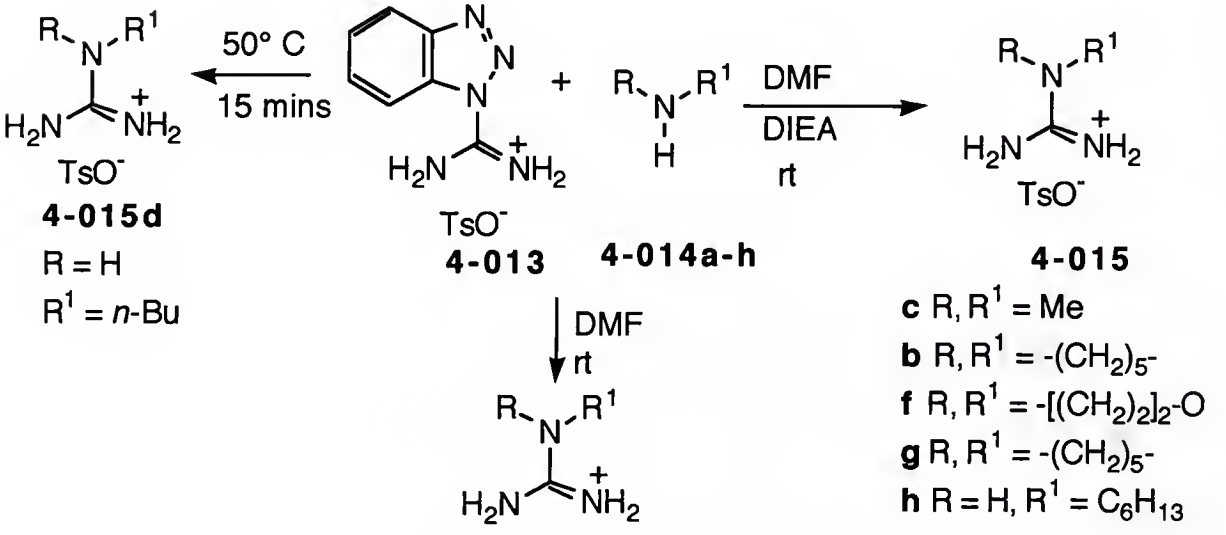
The reaction for the formation of guanidines from benzotriazole-1-carboxamidinium tosylate (**4-013**) is general for primary and secondary amines including aromatic amines. Reactions are conveniently carried out using one molar equivalent each of **4-013** and the amine (i) in dimethylformamide (DMF) in the presence or absence of diisopropylethylamine

(DIEA) at room temperature, (ii) in CH_3CN or (iii) in the absence of solvent. Product isolation is facile as the precipitated guanidine can be filtered from the ether soluble benzotriazole by-product when DMF is used as solvent. When CH_3CN is employed the product precipitates during the reaction, while in the absence of solvent the product can be isolated chromatographically (Scheme 4-2, Table 4-1).



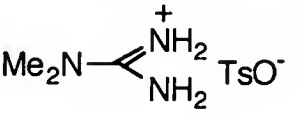
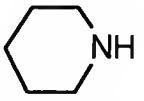
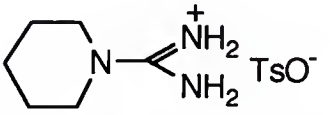
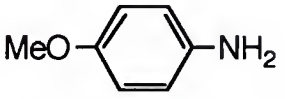
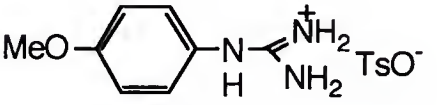
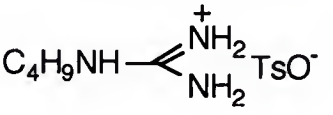
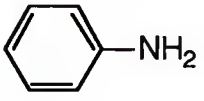
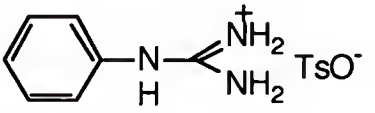
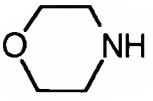
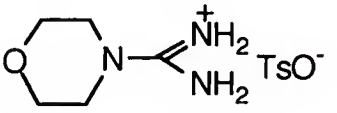
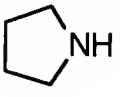
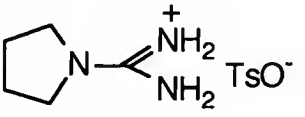
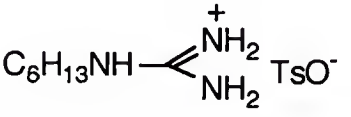
4-001 **4-012** **4-013**

Scheme 4-1



Scheme 4-2

Table 4-1. Products of the Reaction of Benzotriazole-1-carboxamidinium Tosylate (**4-013**) with Primary and Secondary Amines

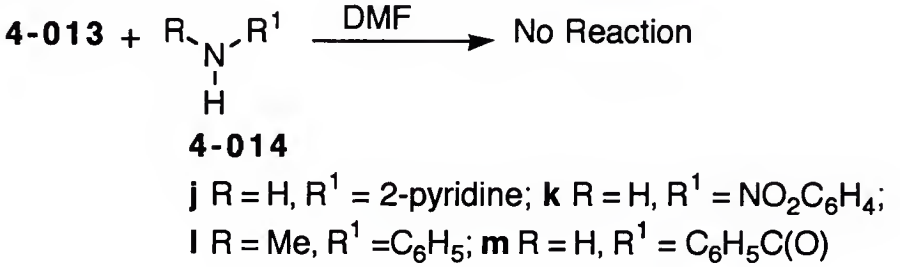
Entry	Amine **4-014a-h**	Guanidine **4-015a-h**	Yield(%)[a]
(i)	Me_2NH		69[b]
(ii)			84[b]
(iii)			68[c]
(iv)	$C_4H_9NH_2$		55[d]
(v)			68[e]
(vi)			86[f]
(vii)			71[f]
(viii)	$C_6H_{13}NH_2$		67[f]

[a]Reported yields for purified compounds, [b]reaction time 4-5 h, [c]reaction time 24 h, performed in the absence of DIEA (diisopropylethylamine), [d]reaction time 15 min in the absence of solvent, [e]reaction time 5 days, performed in CH_3CN in the absence of DIEA, [f]reaction time 24 h.

Formation of the guanidines **4-015a-b**, and **4-015f-h** was carried out in DMF in the presence of DIEA (Scheme 4-2, Table 4-1). In these reactions DIEA serves to neutralize **4-013** and make it more miscible with organic solvents. Use of the primary amine **4-014h** and the secondary amines **4-014a** and **4-014f-g** afforded the desired guanidines easily. However, when the secondary amine, *N*, *N*-diethylamine (**4-014i**) was used, this resulted in the formation of the tosylate salt **4-016** and not the desired guanidine (Scheme 4-3). This may be because *N*, *N*-diethylamine is a sterically hindered, more basic secondary amine.

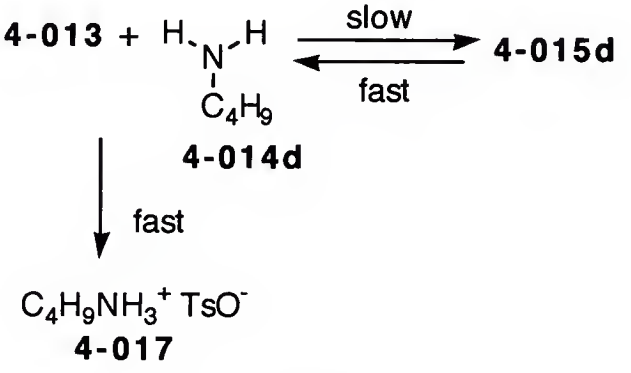
Scheme 4-3

4-Methoxyaniline-1-carboxamidinium tosylate (**4-015c**) and aniline-1-carboxamidinium tosylate (**4-015e**) were both prepared from **4-013** in DMF in the absence of DIEA. With primary aromatic amines, the absence of DIEA does not hinder the reaction. Guanidine **4-015e** could also be synthesized in CH_3CN after five days stirring at room temperature. Attempts were made to generate various other phenyl substituted guanidines under the above conditions, but resulted in the recovery of unreacted starting materials (Scheme 4-4).



Scheme 4-4

Since previous attempts to generate *n*-butylamine-1-carboxamidinium tosylate (**4-015d**) by the standard procedure using **4-013** in DMF with DIEA resulted either in poor yield (34%) or isolation of the corresponding *n*-butylamine tosylate salt (**4-017**), it was prepared in the absence of solvent. Guanidine **4-015d** was prepared by heating **4-013** and **4-014d** at 50 °C for 15 minutes. The product was purified by column chromatography. The poor yield isolated in the standard procedure may be due to reversible formation of the desired product, which can then decompose to starting materials and undergo formation of the tosylate salt at a much faster rate (Scheme 4-5).



Scheme 4-5

Comparisons of the existing literature methods for the preparation of guanidines from amines suggest that the pyrazole-1-carboxamidine (**4-007**) [92JOC2497] approach is superior to the other literature methods previously mentioned. Some of the advantages include mild reaction conditions, the ease of preparation and product isolation and the extended shelf-life of the parent amidine.

We therefore compared benzotriazole-1-carboxamidinium tosylate (**4-013**) with the pyrazole derivative **4-007** and concluded that **4-013**, while similar in ease of preparation and isolation and in shelf-life stability, does offer advantages over **4-007** in terms of yields and increased reactivity. Thus, the hydrochloride derivative of piperidine-1-carboxamidinium tosylate (**4-015b**) was reported to be prepared in 71% isolated yield

from pyrazole-1-carboxamidine hydrochloride (**4-007**) [92JOC2497]. We now report a yield of 84% using **4-013**. Preparation of the hydrochloride derivative of 4-methoxyaniline-1-carboxamidinium tosylate (**4-015c**) using pyrazole-1-carboxamidine hydrochloride (**4-007**) [92JOC2497], required a reaction time of 21 h to give a yield of 58%. Using the benzotriazole methodology, an improved yield of 68% was isolated after a reaction time of 24 h. The benzotriazole derivative **4-013** is more reactive than **4-007**, which is as expected, since benzotriazole is a better leaving group than pyrazole [91T2683]. The hydrochloride analog of the phenylguanidine salt **4-015e** was prepared previously from aniline using **4-007** [92JOC2497], but the procedure involved refluxing in nitrobenzene. The use of **4-013** afforded **4-015e** in dimethylformamide or acetonitrile after 5 days at room temperature.

Conclusions

In summary, benzotriazole methodology has been extended in the preparation of an alternative reagent for the preparation of guanidines from primary aliphatic and aromatic amines and secondary aliphatic and cyclic amines. Guanidines can be conveniently prepared and isolated in a one pot sequence as the corresponding tosylate salts. This eliminates the step of converting the guanidine to an isolable compound such as a picrate. Under mild conditions, benzotriazole-1-carboxamidinium tosylate (**4-013**) gives guanidines in moderate to good yields, and offers advantages such as increase yields and reactivity over the existing procedure employing pyrazole-1-carboxamidine hydrochloride (**4-007**). Benzotriazole-1-carboxamidinium tosylate (**4-013**) can be easily prepared and purified and stored over long periods of time.

Experimental

General. Melting points were obtained using a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded either on a Varian VXR 300 (300 MHz), Gemini (300 MHz) or General Electric QE 300 (300 MHz) spectrometer. ^{13}C NMR were recorded at 75 MHz on the same instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard. Coupling constants (*J* values) are reported in Hz. All reactions were performed in an inert atmosphere using oven-dried glassware. Elemental analyses and high resolution mass spectrometry were performed on site at the analytical facility.

Benzotriazole, ether and piperidine were purchased from Fisher and used as supplied. DMF, also purchased from Fisher, was dried over 4Å molecular sieves. Cyanamide, dimethylamine, *n*-butylamine, pyrrolidine, *n*-hexylamine and DIEA were purchased from Aldrich and used as supplied. Aniline (Aldrich) was distilled prior to use. 4-Methoxyaniline (Aldrich) was recrystallized from hexane prior to use. Morpholine (Fluka) was used as supplied. TLC was performed on pre-coated silica gel F254 plates which were developed using hexane:ether (70:30) and were visualized with UV light and iodine.

Benzotriazole-1-carboxamidinium Tosylate (**4-013**). A mixture of benzotriazole (11.9 g, 0.1 mol), cyanamide (4.2 g, 0.1 mol) and *p*-toluenesulfonic acid (19.2 g, 0.1 mol) was refluxed in 1,4-dioxane (150 mL) for 24 h. A white precipitate formed upon heating. The reaction was then cooled to room temperature, diluted with Et_2O (200 mL) and stirred vigorously for several hours. The solid was filtered under vacuum, allowed to air dry, then recrystallized from benzene/EtOH (50:50) and dried *in vacuo*. Fine white needles (25.6 g, 77%) were isolated, mp 181-183 °C. ^{1}H NMR (DMSO-d_6): δ = 2.3 (s, 3H), 7.2 (d, 2H, *J* = 7.6), 7.5 (d, 2H, *J* = 8.1), 7.6 (t, 1H, *J* = 7.3), 7.8 (t, 1H, *J* = 7.3),

8.0 (d, 1H, J = 8.4), 8.3 (d, 1H, J = 8.2), 10.1 (br s, 4H). ^{13}C NMR (DMSO-d_6): δ = 20.9, 112.9, 120.4, 125.5, 126.7, 128.4, 130.6, 130.7, 138.4, 144.6, 145.8, 152.0. Further confirmation was accomplished by single x-ray crystallography (see Appendix C).

General procedure for the formation of substituted guanidines

N,N'-Dimethylamine-1-carboxamidinium tosylate (**4-015a**). To a mixture of dimethylamine (40% wt. soln. in water) (100 μL, 90 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and diisopropylethylamine (DIEA) (347 μL, 258 mg, 2.0 mmol) was added DMF (10 mL). The reaction was stirred at room temperature and monitored by TLC. After 5 h the reaction mixture was diluted with Et_2O (20 mL), stirred and the crude precipitate collected, washed with Et_2O and dried. Recrystallization from EtOH afforded white prisms (356 mg, 69%), mp 173-175 °C (lit. [51JCS1252] mp 179 °C). ^{1}H NMR (DMSO-d_6): δ = 2.3 (s, 3H), 2.9 (s, 6H), 7.11 (d, 2H, J = 8.0), 7.3 (s, 4H), 7.5 (d, 2H, J = 8.1). ^{13}C NMR (DMSO-d_6): δ = 20.9, 37.8, 125.5, 128.4, 138.4, 144.7, 156.9.

Piperidine-1-carboxamidinium tosylate (**4-015b**). Treatment of piperidine (296 μL, 255 mg, 3.0 mmol), benzotriazole-1-carboxamidinium tosylate (1.0 g, 3.0 mmol) and DIEA (521 μL, 387 mg, 3.0 mmol) as described for compound **4-015a** gave the crude product after 4 h. Crystallization from EtOH gave fine white needles (753 mg, 84%), mp 183-184 °C. ^{1}H NMR (DMSO-d_6): δ = 1.4-1.5 (m, 6H), 2.3 (s, 3H), 3.4 (t, 4H, J = 5.0), 7.2 (d, 2H, J = 8.4), 7.3 (s, 4H), 7.5 (d, 2H, J = 8.2). ^{13}C NMR (DMSO-d_6): δ = 20.8, 23.2, 25.0, 46.2, 125.5, 128.3, 138.4, 144.8, 155.6. $C_{13}H_{21}N_3O_3S$ requires: C, 52.15; H, 7.07; N, 14.04. Found: C, 52.47; H, 7.17; N, 13.96.

4-Methoxyaniline-1-carboxamidinium tosylate (**4-015c**). Treatment of 4-methoxyaniline (393 mg, 3.0 mmol) and benzotriazole-1-carboxamidinium tosylate (1.0 g, 3.0 mmol) as described for compound **4-015a** gave the crude product after 24 h. Crystallization from MeOH/Et_2O gave fine white needles (884 mg, 68%), mp 143-144 °C. ^1H NMR (DMSO-d_6): δ = 2.3 (s, 3H), 3.8 (s, 3H), 6.9 (d, 2H, *J* = 4.4), 7.2 (d, 4H, *J* = 4.4), 7.3 (s, 4H), 7.5 (d, 2H, *J* = 3.7), 9.5 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 20.9, 55.4, 114.9, 125.5, 127.2, 127.5, 128.4, 138.5, 144.6, 156.3, 158.1. HR MS ($C_{14}H_{19}N_3O_4S$, FAB): $(M+H)^+$ = 166.0910. $C_8H_{12}N_3$ (calcd as free base) requires 166.0980.

n-Butylamine-1-carboxamidinium tosylate (**4-015d**). Benzotriazole-1-carboxamidinium tosylate (3.0 g, 9.0 mmol), *n*-butylamine (887 μL, 657 mg, 9.0 mmol) and DIEA (1.56 mL, 1.16 g, 9.0 mmol) were heated (50 °C) with stirring for 15 minutes. The viscous, pale-yellow crude material was cooled to room temperature, dissolved in a minimal amount of THF and purified by flash column chromatograghy using Et_2O, THF and EtOH consecutively as eluents. The hygroscopic white solid obtained upon evaporation of the EtOH fractions was suspended in $CHCl_3$ to precipitate the pure hygroscopic white solid (1.4 g, 55%), mp 135 °C (decomposition). ^1H NMR (DMSO-d_6): δ = 0.9 (t, 3H, *J* = 5.4), 1.3 (septet, 2H, *J* = 7.5), 1.4 (septet, 2H, *J* = 7.1), 2.3 (s, 3H), 3.1 (q, 2H, *J* = 6.4), 7.1 (d, 2H, *J* = 7.2), 7.6 (d, 2H, *J* = 7.2), NH protons not observed. ^{13}C NMR (DMSO-d_6): δ = 13.4, 19.2, 20.8, 30.4, 40.5, 125.4, 128.2, 138.3, 144.3, 156.8. HR MS ($C_{12}H_{21}N_3O_3S$, FAB): $(M+H)^+$ = 116.1186. $C_5H_{13}N_3$ (calcd as free base) requires 116.1187.

Aniline-1-carboxamidinium tosylate (**4-015e**). Benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and aniline (182 μL, 186 mg, 2.0 mmol) were suspended in CH_3CN (3 mL) and stirred at room temperature for 5 days. The crude precipitate was

filtered and recrystallized from EtOH/Et_2O to yield a fine white powder (417 mg, 68%), mp 150-151 °C. ^1H NMR (DMSO-d_6): δ = 2.3 (s, 3H), 7.1 (d, 2H, *J* = 7.3), 7.2 (d, 2H, *J* = 8.0), 7.3 (d, 2H, *J* = 7.4), 7.4, (t, 1H, *J* = 7.1), 7.5 (d, 2H, *J* = 8.2) 9.7 (s, 1H), NH_2 not observed. ^{13}C NMR (DMSO-d_6): δ = 20.9, 124.4, 125.5, 126.4, 128.4, 129.7, 135.4, 138.4, 144.6, 155.8. HR MS ($C_{14}H_{17}N_3O_3S$, FAB): $(M+H)^+$ = 136.0854. $C_7H_{10}N_3$ (calcd as free base) requires 136.0874.

Aniline-1-carboxamidinium tosylate (**4-015e**). Treatment of benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and aniline (182 μL, 186 mg, 2.0 mmol) in CH_3CN as described for compound **4-015a** gave the crude product after 5 days (392 mg, 64%). HR MS ($C_{14}H_{17}N_3O_3S$, FAB): $(M+H)^+$ = 136.0854. $C_7H_{10}N_3$ (calcd as free base) requires 136.0874.

Morpholine-4-carboxamidinium tosylate (**4-015f**). Treatment of morpholine (174 μL, 174 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and DIEA (347 μL, 258 mg, 2.0 mmol) in DMF (3 mL) as described for compound **4-014a** gave the crude product after 24 h. Crystallization from EtOH/Et_2O gave a fine crystalline, white powder (520 mg, 86%), mp 165-167 °C. ^1H NMR (DMSO-d_6): δ = 2.5 (s, 3H), 3.6 (t, 4H, *J* = 4.8), 3.9 (t, 4H, *J* = 5.2), 7.4 (d, 2H, *J* = 8.3), 7.8 (d & s, 6H J_d = 8.2). ^{13}C NMR (DMSO-d_6): δ = 20.8, 45.2, 65.3, 125.5, 128.4, 138.4, 144.7, 156.4. HR MS ($C_{12}H_{19}N_3O_4S$, FAB): $(M+H)^+$ = 130.0973. $C_5H_{12}N_3O$ (calcd as free base) requires 130.0981.

Pyrrolidine-1-carboxamidinium tosylate (**4-015g**). Treatment of pyrrolidine (166 μL, 142 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and DIEA (347 μL, 258 mg, 2.0 mmol) in DMF (3 mL) as described for compound **4-015a** gave the crude product after 24 h. Crystallization from EtOH/Et_2O gave fine, pale-

yellow needles (404 mg, 71%), mp 185-187 °C. ^{1}H NMR (DMSO-d_6): δ = 1.9 (t, 4H, J = 6.6), 2.3 (s, 3H), 3.3 (t, 4H, J = 6.6), 7.2 (d & s, 6H, J_d = 8.0), 7.5 (d, 2H, J = 8.0). ^{13}C NMR (DMSO-d_6): δ = 20.8, 24.7, 46.9, 125.4, 128.3, 138.2, 144.8, 154.3. $C_{12}H_{19}N_3O_3S$ requires: C, 50.51; H, 6.71; N, 14.73. Found: C, 50.51; H, 6.70; N, 14.55. HR MS ($C_{12}H_{19}N_3O_4S$, FAB): $(M+H)^+$ = 114.1025. $C_5H_{12}N_3$ (calcd as free base) requires 114.1031.

n-Hexylamine-1-carboxamidinium tosylate (**4-015h**). Treatment of *n*-hexylamine (264 μL, 202 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and DIEA (347 μL, 258 mg, 2.0 mmol) in DMF (3 mL) as described for compound **4-015a** gave the crude product after 24 h. Crystallization from EtOH/Et_2O gave fine white, crystalline flakes (420 mg, 67%), mp 129-131 °C. ^{1}H NMR (DMSO-d_6): δ = 0.8 (t, 3H, J = 6.6), 1.2 (br s, 6H), 1.4 (q, 2H, J = 6.3), 2.3 (s, 3H), 3.1 (q, 2H, J = 6.5), 7.2 (d & s, 7H, J_d = 8.2), 7.6 (d, 2H, J = 8.3). ^{13}C NMR (DMSO-d_6): δ = 13.9, 20.8, 22.0, 25.7, 28.3, 30.8, 40.8, 125.4, 128.3, 138.4, 144.5, 156.8. HR MS ($C_{14}H_{25}N_3O_3S$, FAB): $(M+H)^+$ = 144.1431. $C_7H_{18}N_3$ (calcd as free base) requires 130.1501.

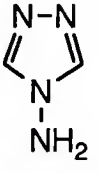
N,N-Diethylamine tosylate salt (**4-016**). Treatment of *N,N*-diethylamine (197uL, 146 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and DIEA (287 μL, 258 mg, 2.0 mmol) in DMF (5 mL) as described for compound **4-015a** gave the crude product after 24 h. Crystallization from EtOH/Et_2O gave fine white, crystalline flakes (470 mg, 82%), mp 96-98 °C. ^{1}H NMR (DMSO-d_6): δ = 1.0 (t, 6H, J = 7.3), 2.15 (s, 3H), 2.7 (q, 4H, J = 7.3), 7.1 (d, 2H, J =7.9), 7.4 (d, 2H, J = 7.8), 8.2 (s, 2H). ^{13}C NMR (DMSO-d_6): δ = 11.0, 20.9, 41.6, 125.5, 128.7, 138.5, 144.7.

n-Butylamine tosylate salt (**4-017**). Treatment of *n*-butylamine (197uL, 146 mg, 2.0 mmol), benzotriazole-1-carboxamidinium tosylate (666 mg, 2.0 mmol) and DIEA (287 μL, 258 mg, 2.0 mmol) in DMF (5 mL) as described for compound **4-015a** gave the crude product after 24 h. Crystallization from EtOH/Et_2O gave fine white, crystalline flakes (380 mg, 68%), mp 80-82 °C. ^{1}H NMR (DMSO-d_6): δ = 0.9 (t, 6H, J = 9.0), 1.3 (m, 2H), 1.5 (m, 2H,), 2.3 (s, 3H), 2.7 (t, 2H, J = 8.5), 7.1 (d, 2H, J = 8.5), 7.5 (d, 2H, 8.5), 7.7 (s, 3H). ^{13}C NMR (DMSO-d_6): δ = 13.8, 19.5, 21.2, 29.4, 39.08, 125.9, 128.6, 138.5, 145.4.

CHAPTER V
INVESTIGATIONS OF 4-AMINO-1,2,4-TRIAZOLE: APPROACHES TO THE DEVELOPMENT OF A NEW ELECTROPHILIC AMINATING AGENT & METHODOLOGY FOR THE PREPARATION OF 4-(ALKYLAMINO)-1,2,4-TRIAZOLES

Introduction

4-Amino-1,2,4-triazole (**5-001**) was first obtained by Curtius and Lang [1888JPR531]. Later in 1906, Bulow and co-workers demonstrated that triazole **5-001** reacts with 1,4-dicarbonyl compounds to afford the corresponding pyrrole derivatives [06CB2618, 06CB4106]. This reaction is characteristic for most primary amines. Triazole **5-001** was also synthesized from the self-condensation of formhydrazide at 150-250 °C [44OS12]. The formhydrazide was made from ethyl formate and hydrazine. The amino group of the triazole **5-001** is weakly basic [71JPR795, 89JOC731], therefore it is alkylated and aminated only at the ring nitrogen atom [89S69]. *N*-Alkylaminotriazoles have been synthesized by the reduction of the corresponding Schiff bases with sodium borohydride and lithium aluminium hydride [88JOC3978].

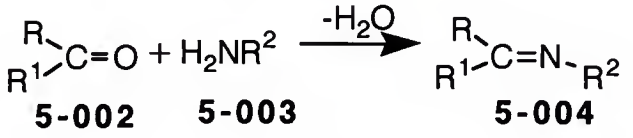


5-001

This chapter, which focuses upon investigations of 4-amino-1,2,4-triazole will be viewed in two parts. The first part will deal with the synthesis of the fluorenyl imine of

5-001 and the second part will focus upon the synthesis of the benzotriazole adduct of **5-001**.

The generation of *N*-substituted imines from primary amines and aldehydes or ketones (Scheme 5-1) plays an important role in the synthesis of aza-aromatic compounds [72MI73] and the biosynthesis of amino acids [83MI].



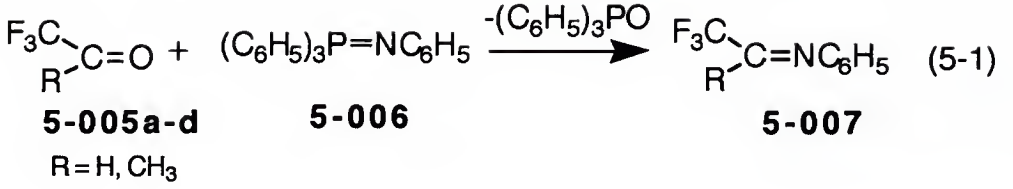
5-002 **5-003** **5-004**

Scheme 5-1

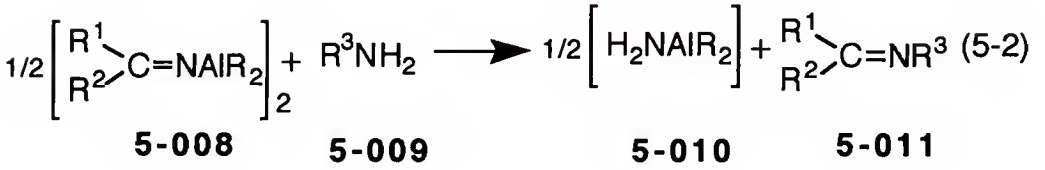
In *vitro* preparation of imines increases in difficulty as one progresses from aldehydes to ketones and as one utilizes aromatic amines instead of aliphatic amines [63CRV493]. Almost 130 years ago, Schiff and co-workers demonstrated that aldimine formation from aromatic amines is base catalyzed [1864ACP118]. Reddelien found that for ketimines bearing two or more aromatic groups, a combination of proton and Lewis acids are required as the catalyst for imination [13CB2721].

More recently, titanium tetrachloride ($TiCl_4$) has been used to promote the formation of ketimines from substituted cyclohexanones [67JOC3246] and the addition of aziridine to ketones [70JOC1861]. A molar equivalent of $n Bu_2SnCl_2$ has been used for the same purpose [82SC495]. Similarly, $ZnCl_2$ has been shown to catalyze the preparation of ketimines from ketones and *N*, *N*-*bis*(trimethylsilyl)amines [66BSF3205].

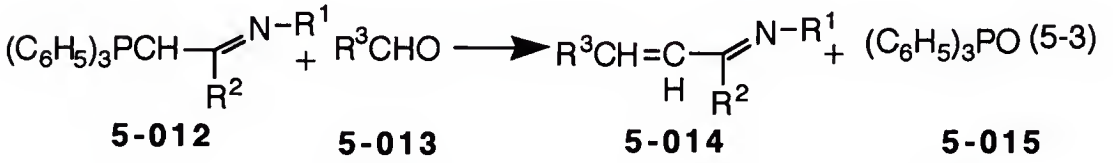
Other indirect routes to ketimines (Scheme 5-2) include the reactions of ketones with iminophosphoranes (Equation 5-1) [66AG(E)947], of *N*-dimethylalkylaluminoimines with primary amines (Equation 5-2) [70LA202] and of α-iminophosphonium methylides with aldehydes (Equation 5-3) [77S626]. Also, Eisch and co-workers have developed *bis*-(dichloroaluminum)phenylimide as a highly selective iminating agent for aldehydes, ketones and acid chlorides (Equation 5-4) [86JOC1848].



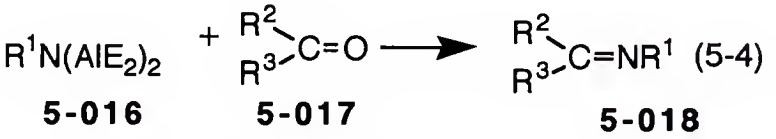
5-005a-d (R = H, CH_3) 5-006 5-007 (5-1)



5-008 5-009 5-010 5-011



5-012 5-013 5-014 5-015

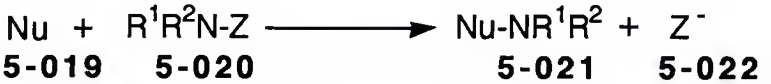


5-016 5-017 5-018

E = Et or Cl, R^2 = alkyl, R^3 = alkyl or H

Scheme 5-2

The development of electrophilic amination has made it possible to transfer amino or substituted amino groups from various aminating agents to various nucleophiles (Scheme 5-3). The most interesting and important structural feature of electrophilic aminating agents of the type R^1R^2N-Z is the attachment of a good leaving group to the NR^1R^2 group. The leaving group Z is displaced by a nucleophile during the amination process.

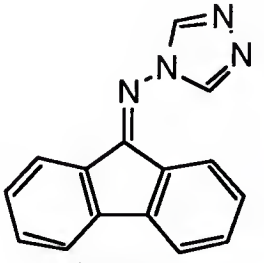


5-019 5-020 5-021 5-022

Scheme 5-3

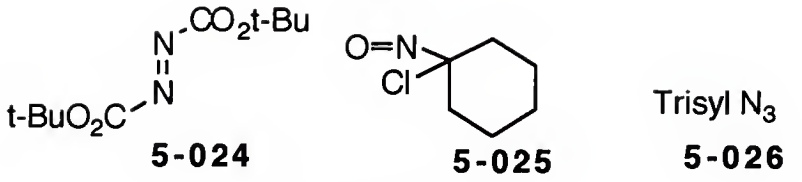
The electrophilic amination of organometallic reagents constitutes an example of "umpolung" methodology for the direct formation of C-N bonds. A detailed review by Erdik and co-workers describes the electrophilic aminating agents commonly used for carbanions [89CRV1947].

The first part of this project focuses on the development of a potentially new electrophilic aminating reagent, *N*-(1,2,4-triazol-4-yl)fluorenimine (**5-023**) which should require one mole of nucleophile and simple hydrolysis to free the desired amine. In this case the triazole group should be a potentially good leaving group which should be easily displaced by nucleophiles.



5-023

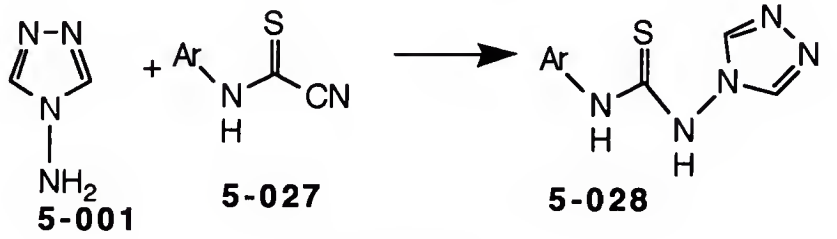
These features would make **5-023** an attractive source of NH_2^+. *N*-(1,2,4-Triazol-4-yl)fluorenimine (**5-023**) would therefore compliment and improve upon commonly used electrophilic aminating reagents such as di-(*tert*-butyl)azodicarboxylate (**5-024**) [86HCA1923, 86JA6394, 86JA6395, 86JA6397], 1-chloro-1-nitrosocyclohexane (**5-025**) [90TL991] and trisyl azide (**5-026**) [90JA4011, 92TL1189] (Scheme 5-4). Previously, the above reagents have been applied to the asymmetric electrophilic amination of ketone enolates. These reagents generally require hydrogenolysis for the release of the protected primary amine group after reaction with a carbon nucleophile.



5-024 **5-025** **5-026**

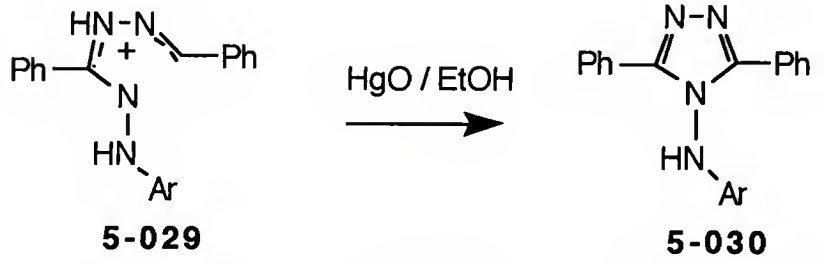
Scheme 5-4

In addition, 4-amino-1,2,4-triazole may be derivatized by reaction with various compounds. The synthesis of substituted 4-amino-1,2,4-triazoles is well documented within the literature. A few examples are noted below. Synthesis of compounds such as **5-028** have been obtained from 4-amino-1,2,4-triazole (**5-001**) and arylisothiocyanates **5-027** [89JHC1735] (Scheme 5-5). *N*-Aminotriazoles have been synthesized by the oxidation of arylidenehydrazidines [77BCJ953] (Scheme 5-6).



5-001 **5-027** **5-028**

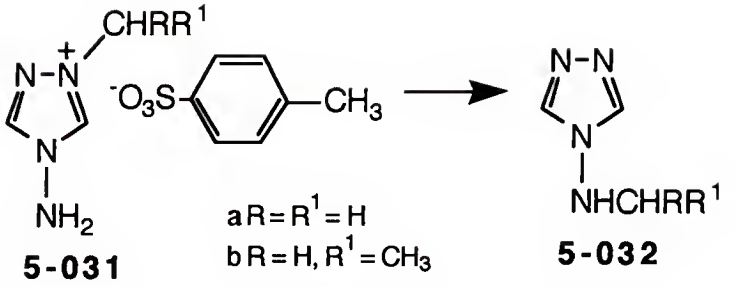
Scheme 5-5



5-029 **5-030**

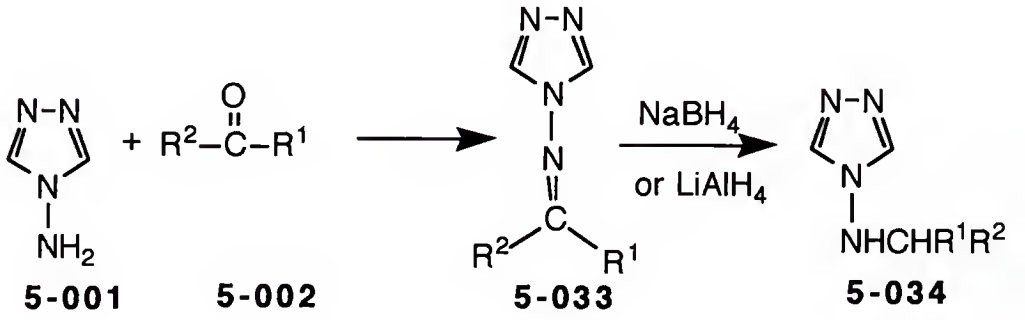
Scheme 5-6

More specifically, 4-(alkylamino)-1,2,4-triazoles have been synthesized from the methyl *p*-toluenesulfonates of cation **5-031a** and the ethyl analogue **5-031b** (Scheme 5-7) [69JPR9].



Scheme 5-7

A second and more convenient method for the synthesis of 4-(alkylamino)-1,2,4-triazoles is the reduction of imines [66MI22]. The reaction of 4-amino-1,2,4-triazole (**5-001**) with appropriate aldehydes or ketones gives the corresponding imines (**5-033**) which can be reduced by $LiAlH_4$ and $NaBH_4$ to give the corresponding 4-(alkylamino)-1,2,4-triazoles (Scheme 5-8).

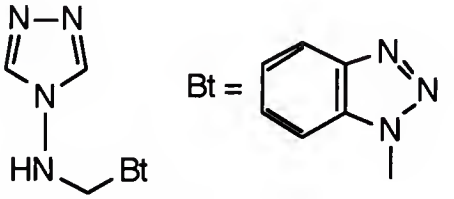


Scheme 5-8

Katritzky and Laurenzo [88JOC3978] used the above methodology to synthesize 4-(alkylamino)-1,2,4-triazoles which were used in the synthesis of alkylaminonitrobenzenes by vicarious nucleophilic amination.

It has been extensively documented that primary and secondary amines can be condensed with benzotriazole to generate a host of benzotriazole adducts. There is also ample documentation that various derivatives can be synthesized by exploiting the leaving group ability of benzotriazole [91T2683]. This second part of this chapter deals with the

synthesis of 4-(alkylamino)-1,2,4-triazoles using 4-amino-1,2,4-triazole (**5-001**) and benzotriazole methodology. The triazole-benzotriazole adduct, 4-(benzotriazol-1-ylmethylamino)-1,2,4-triazole (**5-035**) could be reacted with various Grignard reagents to provide 4-(alkylamino)-1,2,4-triazoles. Using benzotriazole methodology would offer mild conditions for the synthesis of 4-(alkylamino)-1,2,4-triazoles.



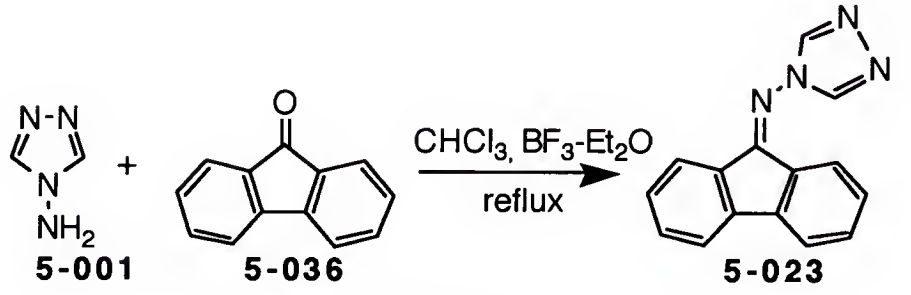
5-035

Results and Discussion

Synthesis of compounds and subsequent reactions of the electrophilic amination will be discussed in this first part of the results. The second part of the results section will focus upon the synthesis and subsequent reactions dealing with the preparation 4-(alkylamino)-1,2,4-triazoles.

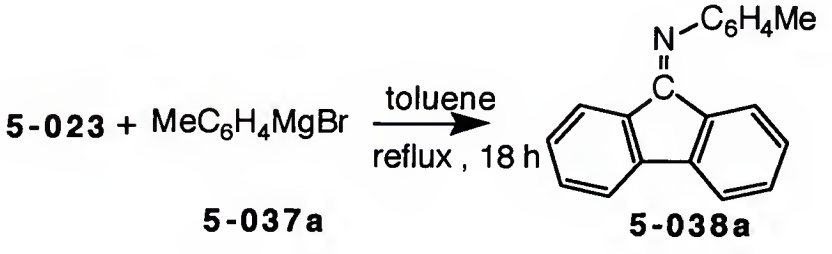
N-(1,2,4-Triazol-4-yl)fluorenimine (**5-023**) was successfully prepared by applying a literature procedure [60JOC940] used to synthesize aromatic fluorenimines. 4-Amino-1,2,4-triazole (**5-001**), fluorenone (**5-036**) and boron trifluoride etherate were refluxed in $CHCl_3$ (Scheme 5-9). After 24 h, removal of the solvent *in vacuo* yielded the crude product which was recrystallized from ethanol. Fine yellow needles (10.4 g, 85%) were isolated (mp 75 °C decomposition). The product was confirmed by ^1H and ^{13}C NMR spectroscopy, low resolution (LR) and high resolution (HR) mass spectrometry and infrared (IR) spectroscopy. The imino carbon was observed at 171 ppm in the ^{13}C NMR. The molecular ion was displayed at *m/z* 246 in the LR mass spectrum and the M^++1 at *m/z*

247 in the HR mass spectrum. The C=N bond was observed at 1723.7 cm^{-1} in the IR spectrum.



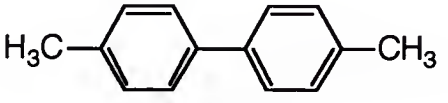
Scheme 5-9

Preliminary solubility tests indicated that neither ether (Et_2O) nor tetrahydrofuran (THF) was a suitable solvent for the electrophilic amination reactions of imine **5-023**. Thus, the initial reactions were performed by dissolving **5-023** (added *via* a Soxhlet extractor) in refluxing toluene, with addition of the preformed Grignard in anhydrous Et_2O. The first reaction investigated was that of 4-tolylmagnesiun bromide (**5-037a**) and imine **5-023** (Scheme 5-10). Thin layer chromatography of the crude reaction mixture indicated that a reaction had taken place, but they were at least five product spots eluting together. After aqueous work-up (using 1M HCl and 10% NaOH) a crude NMR analysis confirmed a complex mixture of products. Column chromatographic separation led to the isolation of three of the five product spots.



Scheme 5-10

The uppermost spot (R_f = 0.68) has been identified as the dimer **5-039** by-product of **5-037a**. The structure of **5-039** was confirmed by ^1H NMR and LR mass spectrometry. In the ^1H NMR spectrum a 3H singlet indicates the methyl group. Within the aromatic region, ranging from 7.2 to 7.5 ppm, two 2H doublets indicate the two sets of CHs of the para-substituted phenyl ring. In this case, the simplicity of the spectrum suggested that the other half of the molecule must be identical with that indicated, and hence the identification of the dimer **5-039**. The molecular ion was observed at *m/z* 182.



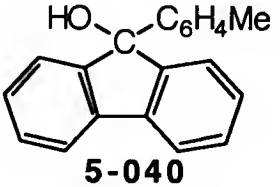
5-039

The next lower spot (R_f = 0.50), which aligns with the starting imine **5-023** was identified as fluorenone (**5-036**) by NMR. The characteristic triplet, doublet, doublet pattern was identical to that of an authentic sample of fluorenone. The ketone carbonyl was clearly evident at 193.7 ppm in ^{13}C NMR spectrum. The presence of fluorenone as a product could indicate one of the following: (a) the starting imine was impure, (b) the reaction was contaminated by water, which hydrolyzed the starting material or (c) under the refluxing conditions in toluene, molecular oxygen was responsible for some peculiar reactions.

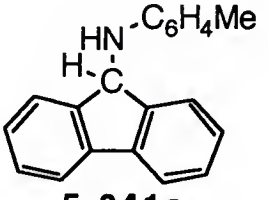
The third spot (R_f = 0.32) was (thought to be) the desired product **5-038a** (Scheme 5-10). A pale yellow oil was isolated in 20% yield. ^1H NMR displays a spectrum supportive of structure **5-038a**. A 3H singlet at 2.2 ppm indicates the methyl group of the phenyl ring. Two 2H doublets in the aromatic region, one at 7.6 and the other at 8.5 ppm indicate the two sets of CHs of the para-substituted phenyl ring, while a multiplet, also within the aromatic region registers the 8H of the fluorenyl- moiety. The ^{13}C spectrum also supports identification of imine **5-038a**, however the 12th carbon peak, the imine carbon failed to be observed (expected around 150-160 ppm) even after a long

acquisition carbon. This may be due to its longer relaxation time, since it is a quaternary carbon. There was also a peak about 84 ppm which was thought to be an impurity since it would indicate a C attached to O, which should not be present. Imine **5-038a**, a known compound [58JOC535] should be a yellow crystalline material. The fact the isolated compound did not readily crystallize, does indicate some impurity. The presence of the unexpected carbon peak at 84 ppm also supports an impurity. The absence of carbon signal about 160 ppm may suggest misinterpretation of the compound.

To further decipher the structure of the compound isolated, low resolution GC/MS analysis was conducted. An intense peak observed (R_t = 22.5 mins) revealed a molecular ion of *m/z* 272, three mass units higher than that of the expected imine **5-038** (*m/z* 269). The even molecular ion ruled out the presence of a single nitrogen, but did not exclude the possibility of an even multiple of nitrogens. Therefore, the compound isolated from Scheme 5-10 was identified as the alcohol **5-040** (*m/z* 272) and not the imine **5-038a** or its reduced product **5-041a**.



5-040
m/z 272



5-041a
m/z 271

With indication of an alcohol (**5-040**) and not the imine (**5-038**), it appears that the products of the reaction are generated from the reaction of the nucleophile with fluorenone and not from the imine **5-023**. The purity of the starting material was checked, to ensure that there was no fluorenone present. CHN analysis was not exact ($C_{15}H_{10}N_4$ requires C 73.14; H 4.10; N 22.76. found C 72.42; H 4.00; N 22.43.), but indicated that the starting material being used to be the imine **5-023**. HR MS analysis revealed an M^++1 of *m/z* 247.0982 for an elemental composition of $C_{15}H_{11}N_4$. The M^++1 is one mass unit

higher than that of imine **5-023** ($C_{15}H_{10}N_4$). From the reaction products it appeared that molecular oxygen was entering into the reaction. This could have been coming from the "in-house" nitrogen used in the reaction. H_2O was ruled out as contaminant, since the Grignard was still active.

Formation of the imine **5-038a**, even in poor yield, would validate the theory that **5-023** may be used as an electrophilic aminating agent (requiring one equivalent of nucleophile). The poor yield was speculated to be due to a combination of the following factors:-

(i) The slow forming Grignard **5-037a**, may not have been fully active, therefore one full equivalent may not have been used.

(ii) It is known from literature reports [61JA3530] that the yields of amines in the reactions of Schiff bases (imines) with Grignards are less than 50% when a 1:1 ratio of RMgX/Schiff base is employed, although quantitative yields may be obtained when 2:1 ratios are employed. This suggests that only half of the available R groups are utilized in the addition of a Grignard reagent across the C=N double bond of the Schiff base (imine).

(iii) The reaction may have proceeded to considerable extent, but inadequate technique for isolation of the "close eluting" spots or decomposition on the column may lead to poor isolated yields.

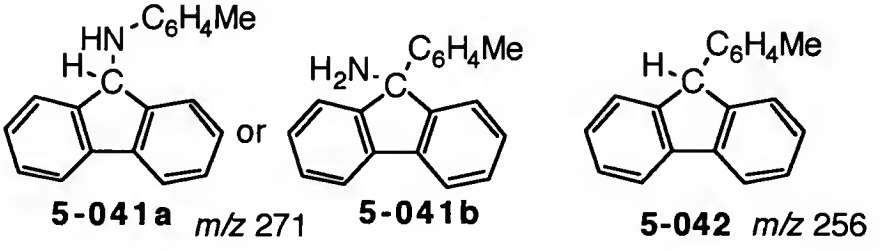
In an attempt to prove or disprove factors (i) and (ii), the reaction (Scheme 5-10) was repeated using 1.6 eq of Grignard reagent. It was expected that the excess of nucleophile would improve the amount of desired product formed. Unfortunately, none of the desired product was detected. Analysis of the reaction mixture by MS revealed three main products:

(i) R_t 16.5 mins, *m/z* 182 (64%)

(ii) R_t 23.3 mins, *m/z* 256 (7%)

(iii) R_t 24.9 mins, *m/z* 271 (7%).

The peak at R_t 16.5 mins was determined to be the dimer **5-039** (as mentioned previously). The significant amount (64%) of dimer **5-039** present indicated that the Grignard prepared was not well formed. Based upon the reactants and reaction conditions the peaks at R_t 23.3 and 24.9 mins were determined to compounds **5-041a** and **5-042**, respectively. Compound **5-041a** indicates two mass units higher (*m/z* 271) than the expected imine **5-038a**, suggesting the reduced structure indicated. The odd molecular ion suggested the presence of a single nitrogen or an odd number of nitrogens. Compounds **5-042** with its mass at *m/z* 256 suggested the absence of nitrogen or the presence of an even number of nitrogens and was determined to be the substituted fluorenone. Another attempt of the reaction indicated the above products to be formed in 37% (**5-041a**) and 33% (**5-042**) by GC/MS.

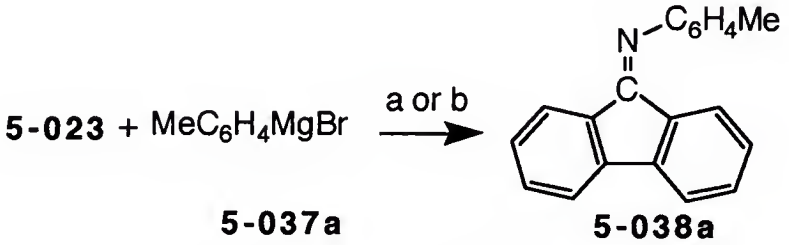


5-041a *m/z* 271 **5-041b** **5-042** *m/z* 256

Amine **5-041a** indicates that azophilic attack is taking place - however, if the imine **5-038a** is formed, reduction probably by the Grignard, could lead to the product **5-041b**. Recently, Morten and co-workers [94TL9225] established that the addition products in Grignard reactions with fluorenone may be obtained *via* the coupling of freely diffusing fluorenone anion radicals with various R radicals. These types of reactions may be possible with the imine **5-038a**, under the refluxing conditions in toluene. The substituted fluorene **5-042**, may be formed from carbophilic attack on the imine carbon, with subsequent removal of the nitrogen moiety, or simply from the reaction of fluorenone.

Due to the complexity of products obtained under the previous conditions, we decided to conduct the reactions using a different inert gas and solvent. It was discovered

that the starting imine dissolves in excess THF with continual stirring. Therefore, two separate reactions each with 1.1 eq of Grignard were performed - one under N_2 and the other under Ar.



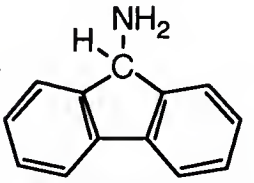
a: THF, N_2, reflux; b: THF, Ar, reflux

Scheme 5-11

Unfortunately after stirring at room temperature for several hours, the reaction under N_2 showed no reaction. Another 1.1 eq of Grignard was added and the reaction was allowed to reflux. The reaction was quenched with MeOH, which led to the isolation of an orange-yellow solid material. GC/MS analysis of the crude material displayed a mixture of products. The main components identified were (i) the desired imine **5-038a** which was not the major product and (ii) fluorenone (**5-036**)/9H-fluorenamine (**5-043**). The component identified as imine **5-038a** was observed as a sharp peak at R_t 24.5 mins, with the molecular ion as base peak at *m/z* 269. The other component had a retention time (R_t 10.3 mins) corresponding to fluorenone (**5-036**), but had a weak M^+ at *m/z* 181, with base peak M^+-1 at *m/z* 180. The M^+-1 (*m/z* 180) could be interpreted as the M^+ of fluorenone. Due to the lack of success with column chromatography - a tedious separation was attempted using preparative TLC. There was some separation of the desired product **5-038a** in very poor yield.

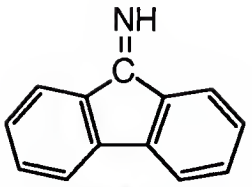
A small amount of dark yellow crystals were recovered (the second band form the solvent front). Analysis by NMR further confirmed the azophilic desired product **5-038a** (see Experimental). ^1H NMR revealed a complex splitting pattern, representative of twelve

aromatic protons, while the ^{13}C spectrum displayed twelve carbons. The most deshielded carbon was observed at 148.5 ppm and was interpreted as the imine carbon. Unfortunately, there was not enough material recovered from the separation to tell definitively between **5-036** and **5-043** by NMR. Other lower spots were recovered as a complex mixture, which the NMR indicated to be mostly aromatic.



5-043 *m/z* 181

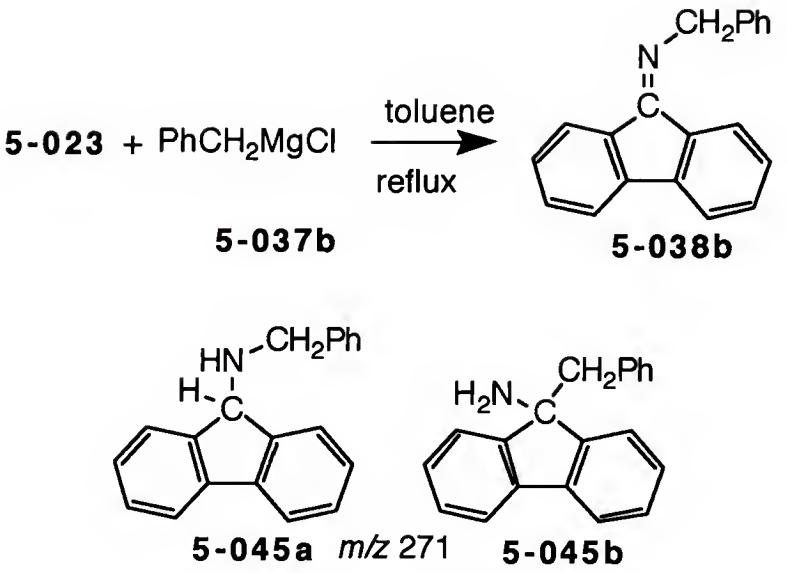
The reaction under argon gas was also quenched with MeOH (Scheme 5-11). GC/MS analysis indicated 25% of the desired azophilic product **5-038a** (R_t 24.4 mins, *m/z* 269), 46% of an unknown (R_t 13.8 mins, *m/z* 220, base peak *m/z* 205) and 29% of *m/z* 179, identified as 9H-fluorenimine (**5-044**). As observed from the reaction under nitrogen, the sharp peak at *m/z* 269 was determined to be the desired azophilic imine **5-038a.** The unknown at *m/z* 220 would indicate a compound without nitrogen, or an even number of nitrogen. The loss of 15 mass units suggest the presence of a methyl group. The mass *m/z* 220 is hard to explain under these reaction conditions since extreme care was taken to exclude molecular oxygen and water. Separation was attempted by column chromatography on alumina - but was not very successful. About 30 mg of a yellowish solid recovered by ^1H NMR supported identification of 9H-fluorenime (**5-044**). A 2H triplet was observed at 7.3ppm and two 1H doublets were observed at 7.5 and 7.7 ppm. Additional separation of these close running spots by HPLC was futile.



5-044 *m/z* 179

Previous work by Katzenellenbogen and co-workers [89JOC2204] indicates that with fluorenimines, carbophilic and azophilic attack are competing reactions. With *n*-butyllithium (*n*-BuLi)as the nucleophile, when the nitrogen substituent in the imine is aliphatic - exclusive azophilic attack occurs. In contrast, when the nitrogen substituent in the imine is aromatic, the amount of azophilic attack decreases (as low as 25%) and the amount of carbophilic attack becomes significant. Such may be the case with imine **5-023**, where the triazole ring is an aromatic moiety.

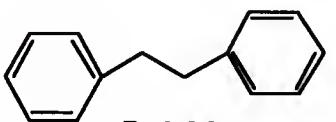
The second electrophilic amination reaction was performed with benzylmagnesium chloride (**5-037b**) (Scheme 5-12). Column chromatographic separation led to the isolation of 5% of product. The compound has been identified as **5-045b** based upon its ^{1}H NMR spectrum which displays a total of 17H, 15 of which are observed in the aromatic region (7.0-8.6 ppm). The desired imine **5-038b** has been ruled out, because it would display a total of 12H within the same region. The two additional protons observed in the aromatic region may be an NH_2 group. In the ^{1}H NMR spectrum the methylene 2H singlet is observed at 4.8 ppm. Structure **5-045a** has also been excluded because it would display a 1H singlet between 6 and 7 ppm which was not observed. The ^{13}C NMR shows a prominent peak about 150 ppm, which may indicate a C-N carbon, while the methylene carbon is clearly visible at 43 ppm.



Scheme 5-12

In an effort to generate the desired product the reaction was repeated using 3 eq. of Grignard. As with 4-tolylmagnesium bromide there was a mixture of five product spots eluting together. The second and third spots ran together and no definitive identification could be made.

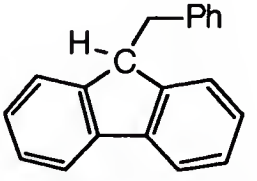
The first spot ($R_f = 0.65$) isolated in 13%, was determined to be the dimer **5-046** by-product of the Grignard **5-037b**. A sharp 2H singlet at 2.8 ppm indicates the methylene protons, while a multiplet is observed in the aromatic region suggesting a monosubstituted benzene. In the ^{13}C NMR, the methylene carbon is observed at 37 ppm, with five aromatic carbons ranging from 125 through 141 ppm. GC/MS analysis indicating a molecular ion of *m/z* 182, led us to the bibenzyl structure **5-046**, since the benzene ring and the methylene group identified from the NMR accounts for only half the mass (*m/z* 91). Isolation of this dimer indicates that the Grignard reagent was not fully active.



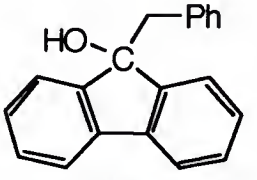
5-046

Spot four (R_f = 0.47), a single spot by TLC, proved to be a mixture of two components by GC/MS. Further investigation by NMR supported two compounds which were determined to be the desired azophilic product **5-038b**, and its reduced derivative **5-045a** (Scheme 5-12). In the proton NMR the methylene protons were observed at 4.7 ppm as a sharp 2H singlet. However, it was evident the desired product was not the only product present. A 1H doublet of singlets was observed about 3.1 ppm (suggesting a CH) and the complex aromatic region integrated 18H instead of 9H. The carbon spectrum also supported two compounds, but with a carbon clearly visible at 160 ppm, interpreted as the imino carbon. Further analysis by GC/MS confirmed what was indicated by the NMR. There was a mixture of two components in a ratio of 3.6:1. The major component was the desired imine **5-038b** with a molecular ion of *m/z* 269 (R_t 24.3 mins), and the minor component was determined to be the reduced derivative (**5-045a**) at two mass units higher (*m/z* 271, R_t 24.5 mins).

Spot five (R_f = 0.25) was interpreted to be **5-047** (*m/z* 256) by NMR, but the GC/MS revealed *m/z* 272 (R_t 22.0 mins) which may be the alcohol product **5-048**. The ^{13}C NMR displayed twelve different carbons. In compliance with the GC/MS the carbon peak at 82 ppm is more suggestive of a carbon bonded to an oxygen and deshielded by an aromatic system. This product **5-048**, from the reaction of the Grignard with fluorenone suggests the presence of fluorenone (**5-036**) as a reactant.



5-047 *m/z* 256



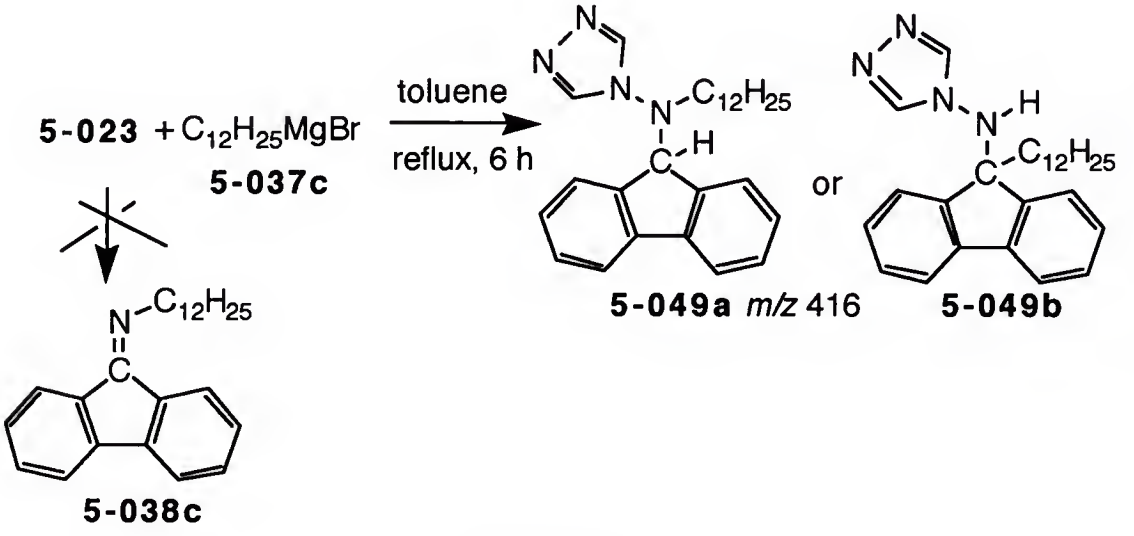
5-048 *m/z* 272

The lone attempt to generate the dodecylimine **5-038c** was unsuccessful in forming the desired product (Scheme 5-13). Once again using the starting imine (added *via* a Soxhlet extractor), **5-023** refluxed in toluene and the Grignard (1 eq.) formed in Et_2O, the reaction was allowed to react for 6 h. The reaction mixture formed a beautiful orange-red color. Quenching with MeOH produced a stronger red color. Concentration of the reaction mixture led to precipitation of a bright orange solid. ^1H NMR analysis of the solid led to strange results. The solid, only partially soluble in $CDCl_3$, displays a well resolved aliphatic region with a 3H multiplet at 0.9 ppm and a broad singlet at 1.3 ppm (≈ 20H) suggesting the presence of the dodecyl chain. However, when obtained in DMSO-d_6, a well resolved aromatic region was displayed indicating triazole CHs (8.5 and 9.0 ppm) and a highly aromatic product. In this case the aliphatic region appears as a series of broad singlets.

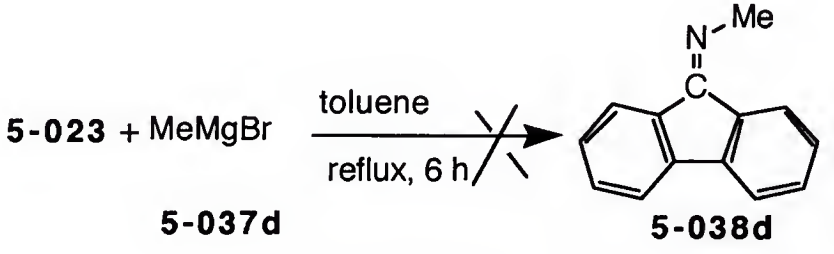
HR MS analysis of the red solid revealed the M^++1 at *m/z* 417.3008 with an elemental composition of $C_{27}H_{37}N_4$. This formula indicated is one unit higher than the structure proposed for compound **5-049** ($C_{27}H_{36}N_4$) (see Scheme 5-13). The presence of four nitrogens suggested that the triazole group was still in place. The base peak was observed at *m/z* 348.2766 ($C_{25}H_{34}N$), representing loss of the triazole moiety. Thus, the compound was determined to be compound **5-049**. The compound is more likely to be **5-049b**, since with aliphatic nucleophiles and aromatic substituents on the imine carbophilic attack tends to be the major reaction pathway. Attack at the carbon center, helps to explain the retention of the triazole moiety, which did not act as a leaving group in this case.

With the unexpected results from the dodecyl nucleophile, we decided to use the methyl derivative **5-037d**, because of its small size. This small nucleophile should afford azophilic attack without the hindrance of a long aliphatic chain or a more bulky substituent. The resulting products should be less complex since these should now be a singlet for the methyl group and the fluorenyl backbone for the aromatic region. Unfortunately, the NMR of the reaction indicated unreacted starting imine **5-023** (Scheme 5-14). There was no

incorporation of a 3H methyl singlet about 3 ppm and a sharp 2H singlet at 8.5 ppm was a clear indication for the presence of the triazole moiety. The ^{13}C NMR indicated only aromatic carbons of the starting imine (see Esperimental).

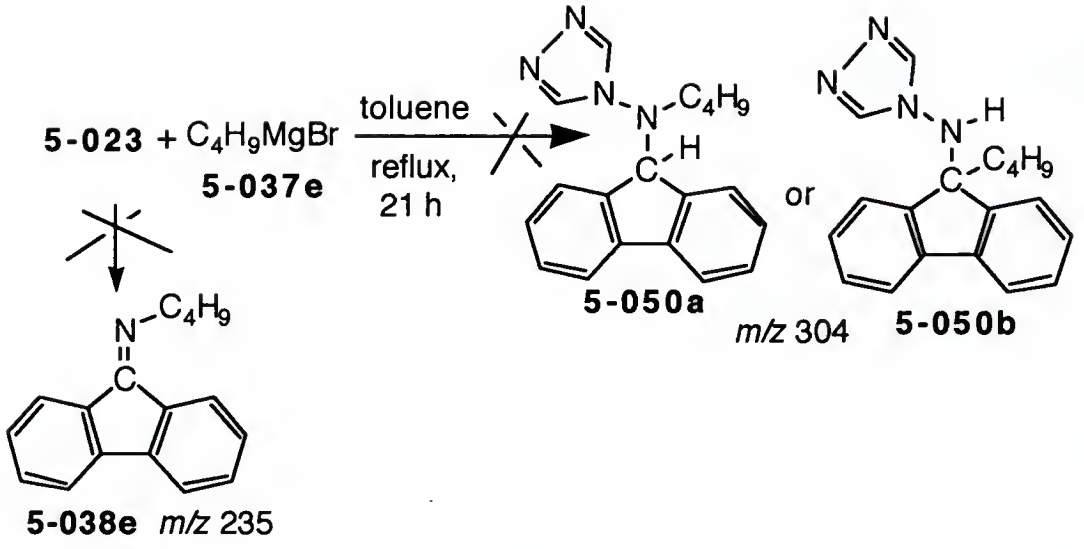


Scheme 5-13



Scheme 5-14

Still investigating the pattern of reactivity for the aliphatic nucleophiles, *n*-butylmagnesium bromide was used. The ^{1}H NMR obtained (in DMSO-d_6), of the redish solid isolated, suggested a highly aromatic product. Surprisingly, a 2H singlet at 9 ppm indicated the presence of triazole CHs, while a 3H singlet about 1 ppm suggested the methyl of the aliphatic group. HR MS of the redish solid isolated, displayed an $M^{+}+1$ of *m/z* 322 ($C_{21}H_{14}N_4$) not the desired imine **5-038e** (*m/z* 235, $C_{17}H_{17}N$), nor the addition product **5-050** (*m/z* 304, $C_{19}H_{20}N_4$) (Scheme 5-15).

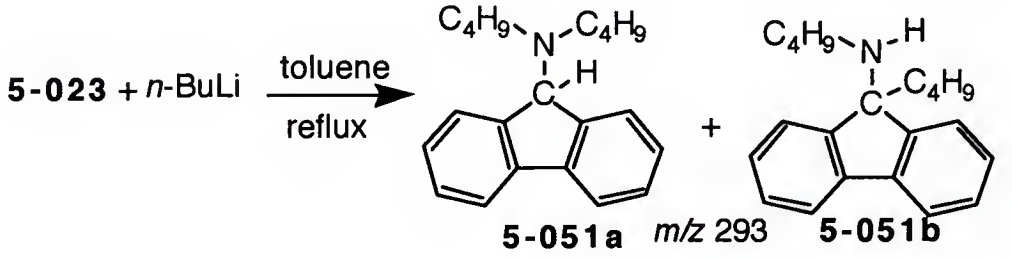


Scheme 5-15

Based upon Katzenellenbogen's findings [89JOC2204], the reaction was conducted with *n*-BuLi (3eq). We wanted to investigate the effect of the metal cation on the product formation in the reaction. With *n*-BuLi and fluorenimines (=N-R), the major product tends to be from azophilic addition when R is aliphatic, and carbophilic when R is aromatic [89JOC2204]. Crude NMR suggested that all the starting imine was consumed. However, GC/MS did not indicate the expected product **5-037e**, but instead a complex mixture of products, particularly the disubstituted product **5-051** with *m/z* 293. That is, many other products displayed a molecular ion of *m/z* 239 with varying base peaks. Excess of the nucleophile accounts for the bis addition product (Scheme 5-16).

With the promising results from the excess nucleophile the reaction was repeated with a single equivalent of *n*-BuLi. Since excess *n*-BuLi led to bis addition, then a single equivalent should offer mono addition and help determine whether azophilic or carbophilic attack was dominant. Unfortunately, after 2 h, GC/MS suggested various carbophilic addition products (*m/z* 220, 222, 278), fluorenone (*m/z* 180) (**5-036**) and 9-fluorenimine (*m/z* 179) (**5-044**) (see previous), but none of the desired imine product **5-038e**. The

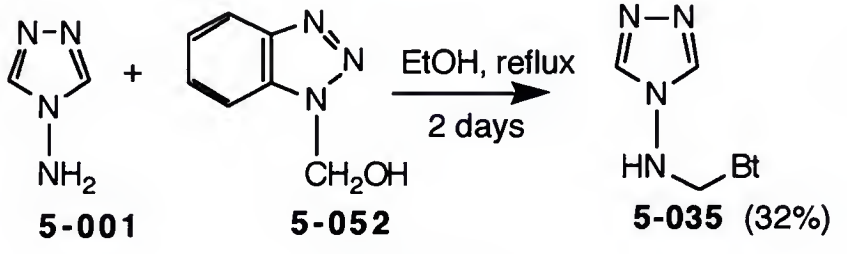
reaction was then allowed to reflux further and GC/MS analysis after 15 h indicated the same series of carbophilic products and only a trace of the desired imine product (<1%).



Scheme 5-16

With the surprising and unexpected results from the above electrophilic amination reactions, we concluded the electrophilic amination investigations and focused then, upon the derivatization of 4-amino-1,2,4-triazole (**5-001**) using benzotriazole methodology. It should be noted here that the data reported is preliminary, therefore the yields and procedures reported have not been optimized. However, the results are extremely promising.

After a number of previous unsuccessful attempts 4-(benzotriazol-1-ylmethylamino)-1,2,4-triazole (**5-035**) was eventually synthesized by refluxing 4-amino-1,2,4-triazole (**5-001**) and hydroxymethylenebenzotriazole (**5-052**) in EtOH (Scheme 5-17). The reaction appears to be a slow one, since only 32% yield of product is isolated after two days of refluxing.



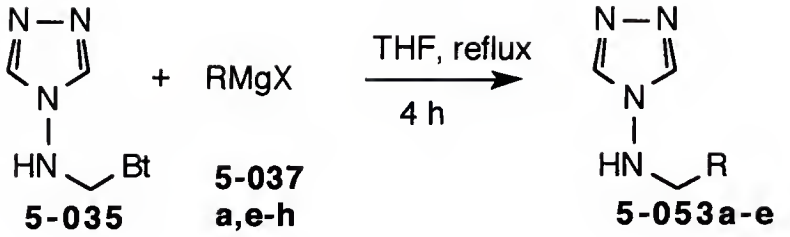
Scheme 5-17

The product was confirmed by ^{1}H and ^{13}C NMR. ^{1}H NMR displays a 2H doublet at 6.0 ppm, indicating the methylene protons which are split by the NH proton of 4-amino moiety. The benzotriazole moiety is seen as the characteristic triplet, triplet, doublet, doublet pattern ranging from 7.4 ppm to 8.0 ppm, and the triazole CHs are observed as a sharp singlet at 8.1 ppm. The NH proton is not observed. In the ^{13}C spectrum the methylene carbon is observed at 63.4 ppm while the triazole CHs, which are equivalent are observed at 142.9 ppm. The benzotriazole carbons display the normal aromatic frequency.

With the preparation of the novel benzotriazole-triazole adduct **5-035**, a series of derivatives were prepared by reaction with various nucleophiles. Nucleophilic displacement of the benzotriazole anion resulted in the formation of 4-(alkylamino)-1,2,4-triazoles. All products were confirmed by NMR and HR MS.

4-(Tolylmethylamino)-1,2,4-triazole (**5-053a**) was synthesized from 4-(benzotriazol-1-methylamino)-1,2,4-triazole (**5-035**) and 4-tolylmagnesium bromide (**5-037a**) (Aldrich) (Scheme 5-18). Removal of the benzotriazole by-product is normally done by washing the organic layer with aqueous NaOH, however both the triazole product and the benzotriazole by-product may be removed this way, and column chromatography was used as the method of purification.

^{1}H and ^{13}C NMR confirmed the desired derivative **5-053a**. ^{1}H NMR displays the methyl protons of the aryl group, a 3H singlet at their characteristic 2.3 ppm, while the methylene protons are seen as a 2H singlet at 4.9 ppm. The phenyl CHs are seen as a pair of doublets ranging from 7.0 to 7.2 ppm, while the triazole CHs are observed at 8.1 ppm. In the ^{13}C NMR the methyl carbon is seen at 20.6 ppm, the methylene carbon at 57.0 ppm and the triazole CHs at 142.4 ppm respectively. HR MS displays the molecular ion at *m/z* 188.1061 with an elemental composition of $C_{10}H_{24}N_4$. The base peak was observed at *m/z* 105.0746 (C_8H_9) and supports the loss of the amino triazole moiety.



5-035 **5-037 a,e-h** **5-053a-e**

Entry	**5-053**	R	X	Eq. of RMgX	% yield
(i)	**a**	tolyl	Br	3	57
(ii)	**b**	iPr	Cl	3	23
(iii)	**c**	t-Bu	Cl	3	15
(iv)	**d**	Me	Cl	2.5	54 (crude)
(v)	**e**	n-Bu	Br	2.5	22 (crude)

Scheme 5-18

4-(2-Methyl-1-propylamino)-1,2,4-triazole **5-053b** was synthesized using **5-035** and isopropylmagnesium chloride (**5-037f**) (Aldrich).(Scheme 5-18). The isolated yield after column chromatography was only 23% and may be due to the lower reactivity of the secondary Grignard. ^{1}H NMR displays a doublet at 1.0 ppm indicating the protons of the two methyl groups, while the 2H doublet at 3.0 ppm indicates the methylene protons. The methine proton of the propyl moiety is seen as a septet at 1.7 ppm. The NH proton is observed at 6.1 ppm, while the triazole CHs are observed at 8.4 ppm. In the ^{13}C spectrum the methyl carbons are seen at 20.0 ppm, the methine carbon at 26.4 ppm and the methylene carbon ar 61.3 ppm. The triazole CHs are observed at 143.1 ppm.

4-(2,2-Dimethyl-1-propylamino)-1,2,4-triazole **5-053c** was attempted using **5-035** and*t*-butylmagnesium chloride (**5-037g**) (Aldrich) according to the previously mentioned procedure. The isolated yield after column chromatography was 15%.

The proton NMR displays double peaks which may suggest a mixture of compounds. The ^{1}H NMR indicates indicates a doublet at 0.5 ppm, which was expected to appear as a singlet for the *t*-butyl protons. Also, the ^{13}C NMR indicates a corresponding

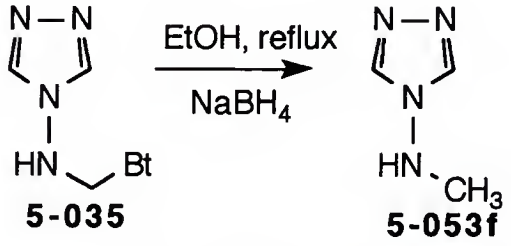
set of carbons at 27.3 ppm and 27.5 ppm which seems to indicate two *t*-butyl groups or non-equivalent methyls of one *t*-Bu group. There are also two peaks in the region which was expected to indicate a single peak for the triazole CHs. HR MS analysis of the isolated compound revealed a mixture, but the major compound displays its molecular ion at *m/z* 154.1252 ($C_7H_{14}N_4$) which would suggest the desired compound **5-053c**, with a single *t*-Bu group.

4-(Ethylamino)-1,2,4-triazole (**5-053d**) was synthesized using **5-035** and methylmagnesium chloride (**5-037h**) (Aldrich) (see Scheme 5-18). Purification was attempted by washing with NaOH (10%) since the yields isolated from column separation were quite low. Unfortunately, after isolating 54% crude yield, washing with NaOH resulted in about 90 mg of pure product. ^1H and ^{13}C NMR confirm triazole **5-053d**, which agrees well with that reported in the literature [88JOC3978]. The methyl 3H singlet was observed at 1.1 ppm (same for the literature), while the methylene 2H quintet was observed at 3.2 ppm (a 2H quartet for the literature). The triazole 2H singlet observed at 8.3 ppm, are found at 8.5 ppm in the literature. The triazole carbons were observed at 143.1 ppm in the ^{13}C NMR.

4-(Pentylamino)-1,2,4-triazole (**5-053e**) was synthesized using **5-035** and *n*-butylmagnesium bromide (**5-037e**) (synthesized) (see Scheme 5-18). As with **5-053d** purification of this compound was attempted *via* washing with aqueous NaOH. An isolated yield of 22% still showed traces of the benzotriazole by-product. However, ^1H and ^{13}C NMR confirm the formation of triazole **5-053e.** ^1H NMR displays the methyl protons at 0.8 ppm as a triplet, while the methylene envelope (6 H) is observed as a multiplet at 1.3 ppm and the methylene protons alpha to the NH are seen at 3.0 ppm as a triplet. Also, both the NH and the triazole protons are seen as singlets at 6.7 ppm and 8.6 ppm respectively.

4-(Methylamino)-1,2,4-triazole (**5-053f**) cannot be obtained *via* nucleophilic displacement of benzotriazole by a Grignard reagent, therefore reduction with $NaBH_4$ was

attempted (Scheme 5-19). Crude ^{1}H and ^{13}C NMR indicated the desired product **5-053f**, which correlates well to that reported in the literature [88JOC3978]. The methyl 3H singlet and the triazole 2H singlet were observed at 3.0 and 8.6 ppm, respectively in the ^{1}H NMR. The methyl and triazole carbons were displayed at 41.7 ppm and 143.1 ppm, respectively in the ^{13}C NMR.



Scheme 5-19

Conclusions

N-(1,2,4-Triazol-4-yl)fluorenimine (**5-023**) has been conveniently prepared by a method based upon the literature procedure [61JOC940] used to synthesize various other fluorenimines. Electrophilic amination reactions have been attempted with quite unexpected and surprising results.

Based on the results obtained from **5-038a** and **5-038b**, it is evident that the basic concept of **5-023** as an electrophilic aminating agent works. However, at this stage it is clear that the desired imines are not the major products of the reactions. The poor isolated yields may be due to insufficient nucleophile concentration, work-up and separation techniques not suited for the imines generated and the numerous competing side reactions.

When the reactions were carried out in toluene under N_2 - it was evident that molecular O_2 was present. This, combined with the reaction conditions may decompose the starting imine. It may also explain the presence of fluorenone and subsequent

nucleophilic products. However, switching to THF and Ar did not decrease the number or the complexity of products formed.

With aromatic Grignards, it appears that azophilic and carbophilic attack are competing reactions. When azophilic attack occurs (on the imine N), subsequent reduction (possibly by the Grignard reagent) of the corresponding imine may explain formation of the fluorenyl amine. On the other hand, it was thought that when carbophilic attack occurred, both the imine N and the triazole group are removed, but those products without N may be from the reaction of fluorenone. With aliphatic Grignards, specifically dodecylmagnesium bromide, HR MS confirms that attack is occurring with retention of the imine N and the triazole system.

Commercial Grignards were used and similar results were obtained as when synthesized nucleophiles were used. Since the desired products were not formed in significant amounts, numerous attempts have been made to isolate and characterize those products which were. These attempts have been without much success. Excess equivalents of nucleophile lead to the formation of different products and not an increase in the amount of desired product formed. GC/MS has been used for the elucidation and confirmation of many of the above results. It should be noted that this method is not a useful synthetic procedure.

For the second part of this chapter, benzotriazole methodology has been formulated for the synthesis of 4-(alkylamino)-1,2,4-triazoles. 4-(Benzotriazol-1-ylmethylamino)-1,2,4-triazole (**5-035**) was synthesized in 32% isolated yield. The nucleophilic displacement with various Grignards have resulted in quite positive, though preliminary results. 4-(Tolylmethylamino)-1,2,4-triazole (**5-053a**) and 4-(2-methyl-1-propylamino)-1,2,4-triazole (**5-053b**) have been synthesized in 57% and 23% respectively. The compound isolated as 4-(2,2-dimethyl-1-propylamino)-1,2,4-triazole (**5-053c**) was verified by GC/MS as containing a single *t*-butyl group. 4-(Ethylamino)-1,2,4-triazole (**5-053d**) and 4-(pentylamino)-1,2,4-triazole (**5-053e**) were purified by aqueous washings

and led to lower yields than with column. 4-(Methylamino)-1,2,4-triazole (**5-053f**) was isolated as the crude material.

Experimental

General. Melting points were obtained using a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded either on a Varian VXR 300 (300 MHz), Gemini (300 MHz) or General Electric QE 300 (300 MHz) spectrometer. ^{13}C NMR were recorded at 75 MHz on the same instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard. Coupling constants (*J* values) are reported in Hz. Reactions were performed in an inert atmosphere under argon or nitrogen gas, using oven-dried glassware. Solutions and anhydrous liquid reagents were dried prior to use: diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene were distilled over sodium benzophenone ketyl. Analytical thin layer chromatography (eluent 70:30, hexanes:ether) was performed using pre-coated silica gel 60 F_{254} plastic plates 0.2 mm thick using iodine as an indicator. Preparative TLC was performed on similar glass plates. Elemental analyses and high resolution mass spectrometry were performed on site at the analytical facility. Low resolution mass spectrometry were performed on a Hewlett Packard 5890 Series II Gas Chromatograph/5972 Series Mass Selective Detector.

N-(1,2,4-Triazol-4-yl)fluorenimine (**5-023**). Fluorenone (9.0 g, 0.05 mol), 4-amino-1,2,4-triazole (4.2 g, 0.08 mol) and boron trifluoride etherate (1.5 ml) was refluxed in chloroform (100 mL) for 24 h. After cooling to room temperature the chloroform was removed *in vacuo* to yield a yellow oil which was precipitated by adding a small amount of ethanol. The crude solid was recrystallized from Et_2O: EtOH (70:30). Fine yellow needles were isolated (10.4 g, 85%) mp 75 °C (decomposition). ^{1}H NMR ($CDCl_3$) δ: 6.4 (d, 1H,

J = 7.8), 7.1 (t, 1H, J = 7.8), 7.4 (t, 1H, J = 7.5), 7.5 (t, 1H, J = 7.5), 7.6 (m, 3H), 7.9 (d, 1H, J = 6.9), 8.3 (s, 2H) (triazole). ^{13}C NMR ($CDCl_3$) δ: 106.4, 120.3, 121.0, 124.2, 126.8, 128.3, 129.0, 133.8, 134.5, 134.6, 138.6, 141.9 (triazole), 144.0, 171.5 (C=N). IR (% T) ν(cm^{-1}): 2922.7, 2724.5, 2361.6, 1723.7 (C=N), 1612.7, 1460.2, 1376.6, 1301.6, 736.0. LR MS M^+ = 246, base peak = 164 (M^+-triazole); HR MS ($C_{15}H_{11}N_4$) M^++1 calcd. 247.0983, found. 247.0982. $C_{15}H_{11}N_4$ requires: C, 73.14; H, 4.10; N, 22.76. Found : C, 72.42; H, 4.00; N, 22.43.

N-(4-Methylphenyl)fluorenimine (**5-038a**). *N*-(1,2,4-Triazol-4-yl)fluorenimine (1.0 g, 4.07 mmol) was suspended (at room temperature) in freshly distilled THF (60 mL) until dissolved, under a steady stream of N_2. Tolylmagnesium bromide (Aldrich) (2.2 eq, 1M) was added dropwise *via* syringe. After 15 h the reaction was quenched with MeOH and concentrated *in vacuo*. The material was purified by preparative TLC (hex:Et_2O, 70:30). the title compound was recovered as dark yellow crystals (164 mg, 15%) mp 120 °C, (Lit. [58JOC535] 122-123 °C). ^{1}H NMR ($CDCl_3$) δ: 2.4 (s, 3H) (CH_3), 6.6 (d, 1H, J = 7.7) (fluorenyl), 6.8 (d, 2H, J = 8.5) (*p*-tolyl), 6.9 (t, 1H, J = 7.7) (fluorenyl), 7.2 (d, 2H, J = 7.1) (fluorenyl), 7.4 (q, 2H, J = 7.3) (fluorenyl), 7.5 (t, 1H, J = 7.4) (flourenyl), 7.6 (d, 2H, J = 7.5) (*p*-tolyl), 7.9 (d, 1H, J = 7.4) (fluorenyl). ^{13}C NMR ($CDCl_3$) δ: 21.0, 118.2, 119.5, 120.1, 123.3, 127.1, 127.6, 128.4, 129.8, 131.6, 131.7, 148.5. LR MS ($C_{20}H_{15}N$) M^+ = *m/z* 269.

Fluorenone (**5-036**). The title compound was recovered as a by-product from the reaction for the formation of **5-038a.** ^{1}H NMR ($CDCl_3$) δ: 7.3 (t, 1H, J = 7.9), 7.4 (d, 2H, J = 7.4), 7.6 (d, 1H, J = 7.3). ^{13}C NMR ($CDCl_3$) δ: 120.2, 124.2, 129.0, 134.1, 134.6, 144.3, 193.7 (C=O). LR MS ($C_{13}H_8O$) M^+ = *m/z* 180.

1,1'-Dimethylbiphenyl (**5-039**). The title compound was recovered as a by-product from the reaction for the formation of **5-038a.** ^{1}H NMR ($CDCl_3$) δ: 2.4 (s, 3H), 7.2 (d, 2H, J = 8.1), 7.6 (d, 2H, J = 8.0). ^{13}C NMR ($CDCl_3$) δ: 21.1, 126.8, 129.4, 136.7, 138.3. LR MS ($C_{14}H_{14}$) M^+ = m/z 182.

9-Hydroxy-9-tolylfluorene (**5-040**). The title compound was recovered as a by-product from the reaction for the formation of **5-038a** (when the reaction was performed in toluene). ^{1}H NMR ($CDCl_3$) δ: 2.3 (s, 2H), 7.1 (d, 2H, J = 8.5), 7.2-7.3 (m, 8H), 7.6 (d, 2H, J = 7.2), OH was not observed. ^{13}C NMR ($CDCl_3$) δ: 21.0, 83.5, 120.0 (2C), 124.7, 125.3, 128.4, 128.8, 128.9, 136.8, 139.5, 140.2, 150.5. LR MS ($C_{20}H_{16}O$) M^+ = m/z 272.

9-Fluorenimine (**5-044**). The title compound was recovered as a by-product from the reaction for the formation of **5-038a.** ^{1}H NMR ($CDCl_3$) δ: 7.3 (t, 2H, J = 8.0), 7.5 (d, 1H, J = 7.9), 7.7 (d, 1H, J = 7.9). LR MS ($C_{13}H_{10}N$) M^+ = m/z 179.

Mixture of *N*-benzylfluorenimine (**5-038b**) and 9-benzylaminofluorene (**5-045a**). *N*-(1,2, 4-Triazol-4-yl)fluorenimine (1.0 g, 4.07 mmol) added via a Soxhlet extractor was refluxed in toluene (freshly distilled). Benzylmagnesium chloride (3 eq, 7.2 mL, 1.7 M {synthesized}) was added *via* syringe. After 15 h the reaction was cooled to room temperature and poured onto cold $NH_4^+Cl^-$ (10 mL) and extracted with Et_2O (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The title compounds were isolated as a mixture after column chromatography as a yellow oil (60 mg, 6%). ^{1}H NMR ($CDCl_3$) δ: 3.1 (d of s, 1H, J = 10), 4.7 (s, 2H) (CH_2), 6.8 (d, 1H, J = 7.7), 7.0-7.3 (m, 10H), 7.5-7.8 (q, d & t, 4H, J = 7.0, 7.4, 7.3), 8.2 (t, 2H, J = 7.4), 8.6 (d of d, 2H, J = 7.4, 7.3). ^{13}C NMR ($CDCl_3$) δ: 42.5, 46.8, 120.0, 121.9, 122.0, 124.0, 126.3, 126.7, 127.4, 127.8, 128.2, 128.5, 128.8, 130.0, 130.3, 130.4, 133.0, 139.0, 148.2,

160.0. LR MS M^+ ($C_{20}H_{15}N$, major) = *m/z* 269, M^+ ($C_{20}H_{17}N$, minor) = *m/z* 271, base peak *m/z* 91 ($PhCH_2$)

9-Amino-9-benzylfluorene (**5-045b**). The title compound was recovered as an oil, as a by-product from the reaction for the formation of **5-038b**. ^1H NMR ($CDCl_3$) δ: 4.8 (s, 2H), 7.0-7.8 (series of m, 12H), 8.2 (d of d, 2H, *J* = 7.2, 7.4), 8.6 (d of d, 2H, *J* = 7.0, 7.3). ^{13}C NMR ($CDCl_3$) δ: 43.0, 120.0, 121.9, 122.4, 124.0, 125.9, 126.6, 127.0, 127.3, 128.5, 128.6, 129.8, 130.3, 133.0, 139.1, 142.0, 160.1. LR MS ($C_{20}H_{17}N$) M^+ = *m/z* 271.

Bibenzyl (**5-046**). The title compound was recovered as an oil, as a by-product from the reaction for the formation of **5-038b**. ^1H NMR ($CDCl_3$) δ: 2.8 (s, 2H), 7.2 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 37.9, 125.8, 128.2, 128.3, 128.4, 141.7. LR MS ($C_{14}H_{14}$) M^+ = *m/z* 182.

9-Hydroxy-9-benzylfluorene (**5-048**). The title compound was recovered as a yellow solid (mp 105 °C) by-product from the reaction for the formation of **5-038b**. ^1H NMR ($CDCl_3$) δ: 3.3 (s, 2H), 7.0-7.3 (series of m, 11H), 7.5 (d, 2H, *J* = 8.0). ^{13}C NMR ($CDCl_3$) δ: 45.7, 82.3, 119.8, 120.0, 124.2, 124.7, 126.3, 127.4, 127.4, 128.4, 128.8, 129.4, 130.7, 130.8, 136.3, 136.6, 139.3, 148.2. LR MS ($C_{20}H_{16}O$) M^+ = *m/z* 272.

9-Dodecylamino-*N*-(1,2,4-triazolyl)fluorene (**5-049a**). *N*-(1,2,4-Triazol-4-yl)fluorenimine (2.0 g, 8.13 mmol) added *via* a Soxhlet extractor was refluxed in toluene (freshly distilled). Dodecylmagnesium bromide (prepared from 195 mg Mg, 2.03 g, 8.13 mmol dodecylbromide in Et_2O {5 ml}) was added *via* syringe. After 2 h the reaction was

quenched with MeOH and concentrated *in vacuo*. Orange yellow crystals (1.7 g, 50%) were isolated. ^{1}H NMR ($CDCl_3$) δ: 0.9 (m, 3H), 1.3 (br. s, ≈ 20H), 3.5 (m, 2H) 7.1-7.8 (series of m, 8H), 8.5 (s, 1H), 9.0 (s, 1H). HR MS ($C_{27}H_{37}N_4$) M^++1 calcd. *m/z* 417.3018, found *m/z* 417.3007; base peak *m/z* 348.2766 ($C_{27}H_{34}N_4$) (M^+ - triazole).

4-(Benzotriazol-1-ylmethylamino)-1,2,4-triazole (**5-035**). 4-Amino-1,2,4-triazole (10.0 g, 0.12 mol) and hydroxymethylenebenzotriazole (17.7 g, 0.12 mol) were refluxed in EtOH (100 ml). After 48 h the reaction was stopped (not complete), cooled to room temperature and the solvent removed *in vacuo*. The resulting white solid was washed with excess methylene chloride until TLC (CH_2Cl_2:EtOAc, 2:1) revealed no more unreacted hydroxymethylenebenzotriazole. A white flaky solid was obtained (8.0 g, 32%), mp 135-137 °C. ^{1}H NMR ($CDCl_3$) δ: 6.0 (d, 2H, J = 5.0) (CH_2), 7.4 (t, 1H, J = 7.6 (Bt), 7.5 (t, 1H, J = 7.6) (Bt), 7.7 (d, 1H, J = 8.3) (Bt), 8.0 (d, 1H, J = 8.3), 8.1 (s, 2H) (triazole). ^{13}C NMR ($CDCl_3$) δ: 63.4 (CH_2), 110.5, 119.2, 124.3, 127.7, 132.7, 142.9 (triazole), 145.3. $C_9H_9N_7$ requires: C, 50.23; H, 4.22; N, 45.56. Found: C, 46.46; H, 4.25; N, 46.92.

General procedure for the preparation of 4-(alkylamino)-1,2,4-triazoles

4-(Tolylmethylamino)-1,2,4-triazole (**5-053a**). 4-(Benzotriazol-1-ylmethylamino)1,2,4-triazole (1.0 g, 4.6 mmol) was refluxed in THF (50 mL) until dissolved. Tolylmagnesium bromide (Aldrich 1.0M) (3 eq, 13.9 mmol, 13.9 mL) was added dropwise *via* syringe. After refluxing for 4 h the reaction was cooled to room temperature, diluted with ethyl acetate (100 mL) and quenched with water. The aqueous layer was adjusted to pH 7 and extracted with ethyl acetate (3X, 50 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was column chromatographed (silica, using CH_2Cl_2: EtOAc:EtOH). A light

colored oil (500 mg, 57%) was isolated. ^{1}H NMR ($CDCl_3$) δ: 2.3 (s, 3H) (CH_3), 4.7 (s, 2H) (CH_2), 7.0-7.1 (d of d & s, 5H, J = 8.0, 1.0) (tolyl CHs & NH), 8.1 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 20.6 (CH_3), 57.0 (CH_2), 128.4, 128.8, 129.3, 138.2, 142.4 (triazole). HR MS ($C_{10}H_{12}N_4$) M^+ calcd. *m/z* 188.1062, found *m/z* 188.1061; base peak *m/z* 105.0746 (C_8H_9) (M^+ - triazole moiety).

4-(2-Methyl-1-propylamino)-1,2,4-triazole (**5-053b**). The title compound was synthesized as a thick oil (150 mg, 23%) from 4-(benzotriazol-1-ylmethylamino)1,2,4-triazole (1.0 g, 4.6 mmol) isopropylmagnesium chloride (Aldrich 2.0M) (3 eq, 13.9 mmol, 6.9 mL), using the above procedure for **5-053a**. ^{1}H NMR ($CDCl_3$) δ: 0.9 (d, 6H, J = 6.6) ($2CH_3$), 1.7 (septet, 1H, 6.7) (CH-Me_2), 2.9 (d, 2H, J = 6.7) (CH_2), 6.1 (s, 1H) (NH), 8.4 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 20.0 ($2CH_3$), 26.4 (CH), 61.2 (CH_2), 143.1 (triazole). HR MS ($C_6H_{12}N_4$) M^+ calcd. *m/z* 140.1062, found *m/z* 140.1099; base peak *m/z* 97.0471 ($C_3H_5N_4$) (M^+ - propyl).

4-(2,2-Dimethyl-1-propylamino)-1,2,4-triazole (**5-053c**). The title compound was synthesized as a thick oil (150 mg, 23%) from 4-(benzotriazol-1-ylmethylamino)1,2,4-triazole (1.0 g, 4.6 mmol) isopropylmagnesium chloride (Aldrich 2.0M) (3 eq, 13.9 mmol, 6.9 mL), using the above procedure for **5-053a**. ^{1}H NMR ($CDCl_3$) δ: 0.9 (s, 9H) ($3CH_3$), 2.9 (d, 2H, J = 7.0) (CH_2), 6.1 (t, 1H, J = 6.9) (NH), 8.4 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 27.2 (*t*-Bu), 31.2 (C), 65.5 (CH_2), 142.9 (triazole). HR MS ($C_7H_{14}N_4$) M^+ calcd. *m/z* 154.1218, found *m/z* 154.1252; base peak *m/z* 97.0481 ($C_3H_5N_4$) (M^+ - *t*-Bu).

4-(Ethylamino)-1,2,4-triazole (**5-053d**). The title compound was synthesized (54% crude yield) from 4-(benzotriazol-1-ylmethylamino)1,2,4-triazole (480 mg, 2.2 mmol) methylmagnesium chloride (Aldrich 3.0M) (2.5 eq, 5.6 mmol, 1.9 mL), using the

above procedure for **5-053a**. The title compound was purified by washing with (10%) NaOH, to give off-white crystals (90 mg, 36%) mp 75-78 °C (Lit mp [88JOC3978] 74-77 °C). ^{1}H NMR ($CDCl_3$) δ: 1.1 (t, 3H, J = 7.1) (CH_3), 3.2 (quintet, 2H, J = 6.6) (CH_2), 5.9 (t, 1H, J = 4.9) NH, 8.3 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 12.5 (CH_3), 47.1 (CH_2), 143.1 (triazole).

4-(Pentylamino)-1,2,4-triazole (**5-053e**). The title compound was obtained crude (26%, yellow oil) from 4-(benzotriazol-1-ylmethylamino)1,2,4-triazole (1.0 mg, 4.6 mmol) methylmagnesium chloride (synthesized 2.0M) (2.5 eq, 5.6 mmol, 1.9 mL), using the above procedure for **5-053d**. ^{1}H NMR ($CDCl_3$) δ: 0.8 (t, 3H, J = 7.0) (CH_3), 1.3 (m, 6H) ($3CH_2$), 3.0 (t, 2H, J = 6.3) (CH_2NH), 6.7 (br. s, 1H) NH, 8.6 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3), 21.8 (CH_2), 26.7 (CH_2), 28.3 (CH_2) 52.6 (CH_2NH), 143.1 (triazole).

4-(Methylamino)-1,2,4-triazole (**5-053f**). 4-(Benzotriazol-1-ylmethylamino)-1,2,4-triazole (1.0 g, 4.6 mmol) was refluxed in EtOH with sodium borohydride (3 eq, 528 mg, 13.9 mmol). After 4 h the reaction was cooled to room temperature, quenched with Na_2CO_3 and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. A pale yellow oil (205 mg, 52%) was isolated (small traces of Bt). ^{1}H NMR ($CDCl_3$) δ: 3.0 (s, 3H) (CH_3), 8.6 (s, 2H) (triazole CHs). ^{13}C NMR ($CDCl_3$) δ: 41.7 (CH_3), 143.1 (triazole).

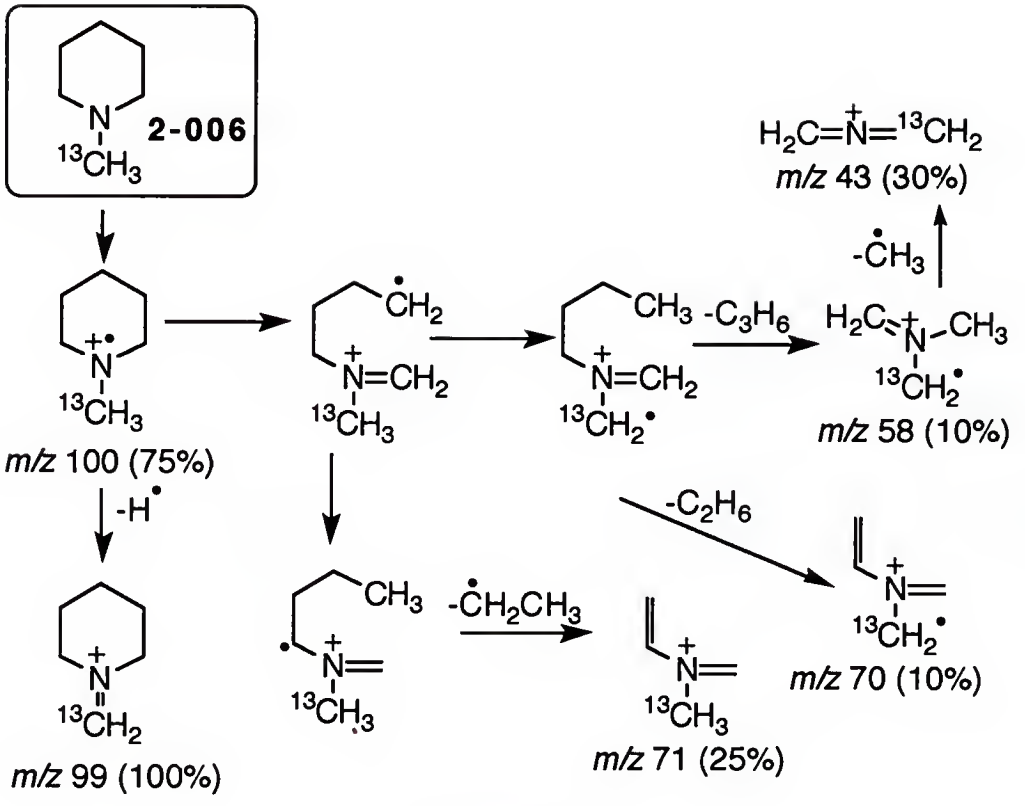
APPENDIX A
MASS SPECTRAL FRAGMENTATION PATTERNS OF PIPERIDINE PRODUCTS

Interpretation of mass spectral fragmentations

Compounds identified in Chapter II, for which no published MS data was available are represented below. The products were assigned structures based upon their MS fragmentation patterns, along with consideration of the reaction conditions, starting materials and a reasonable mechanistic pathway for their formation from the starting materials (see Table 2-4). The authentic compounds (**2-009**, **2-013**, **2-019** and **2-024**) synthesized are also represented. In the following fragmentation schemes fragment ions detected by GC/MS analyses are represent by their mass units (*m/z*).

Fragmentation of *N*-(^{13}C)-methylpiperidine (**2-006**) (Scheme A-1)

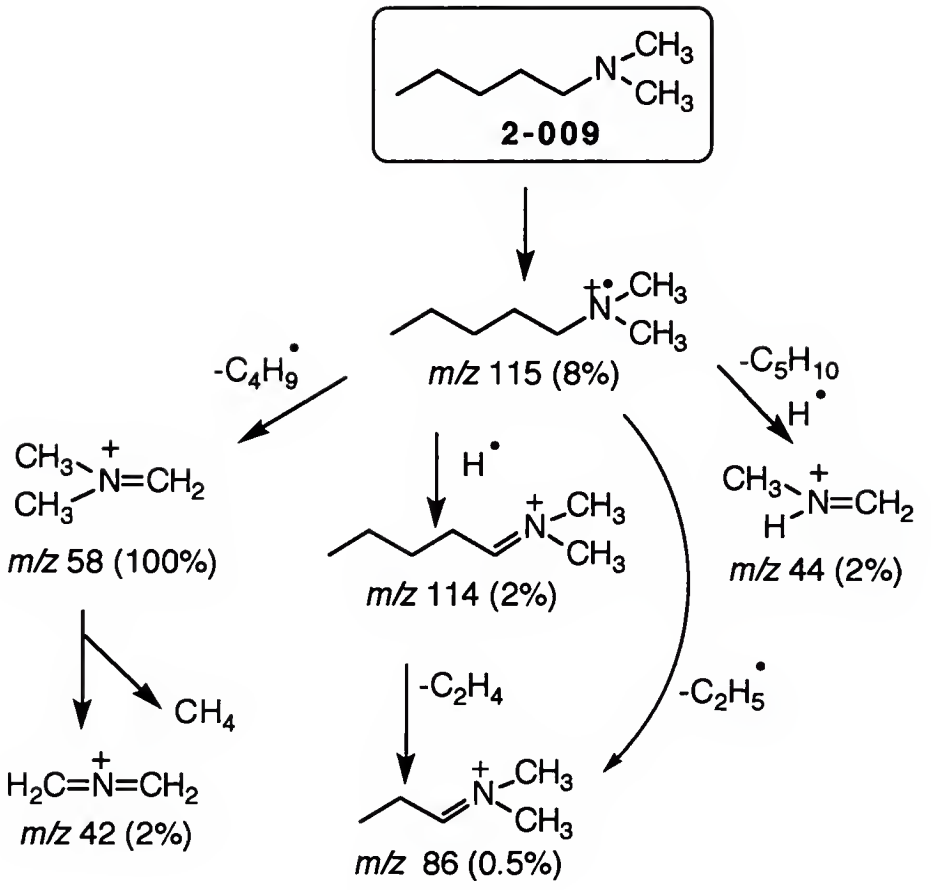
1-(^{13}C)-Methylpiperidine (**2-006**) (Scheme A-1) has the same retention time as 1-methylpiperidine (**2-007**) and its molecular ion appears at *m/z* 100 (75%) [r.i. relative intensity]. The fragmentation pattern (Scheme A-1) is identical to that of **2-007** except that fragments still containing the exocyclic carbon shows peaks at 1 mass unit higher than those for **2-007**. Loss of a hydrogen radical from the molecular ion leads to the base peak at *m/z* 99. The subsequent fragmentation shown in Scheme A-1 is based on that given in reference [B-71MI365, B-67MI313, 66MI681] except there is no documentation for the ion at *m/z* 70.



Scheme A-1

Fragmentation of *N,N*-dimethylpentylamine (**2-009**) (Scheme A-2)

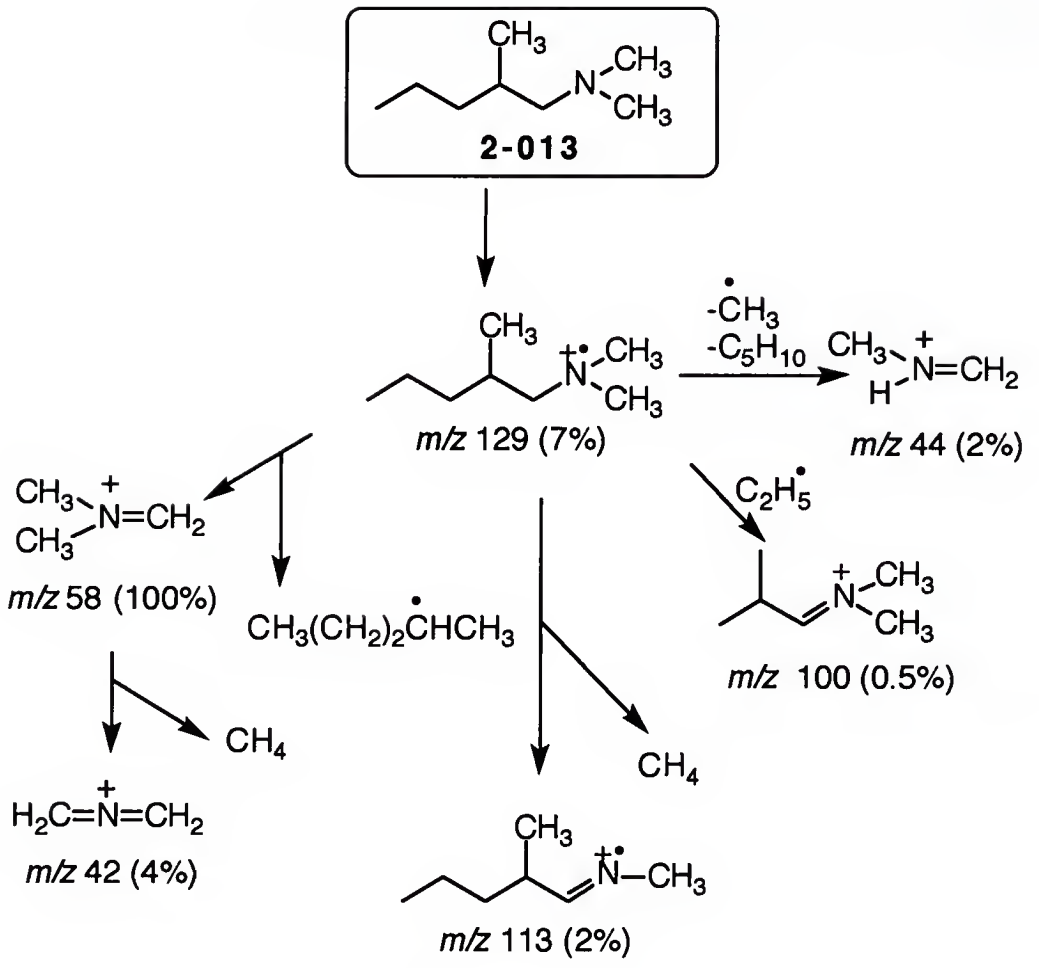
N,N-Dimethylpentylamine (**2-009**) (Scheme A-2), (which was previously synthesized by Swann 43MI165), shows its major fragmentation in the mass spectrometer as an α-cleavage (cleavage of the carbon-carbon bond adjacent to the nitrogen atom), to give its base peak at *m/z* 58, with the subsequent loss of an *n*-butyl radical. The removal of an electron from the lone pair on the nitrogen, is the trigger for simple α-cleavage and results in the formation of an alkyl radical [B-67MI297]. This ion can further fragment to the ion of *m/z* 42. The M-1 fragment at *m/z* 114 is only of weak intensity (2%). The ion at *m/z* 86 is a result of a γ-cleavage with the subsequent elimination of an ethyl radical or loss of ethylene from the M-1 ion. Surprisingly, the intensity for the fragment resulting from β-cleavage was too weak to be observed. Loss of the C-5 neutral gives the ion at *m/z* 45 which then loses a hydrogen radical to give the ion at *m/z* 44.



Scheme A-2

Fragmentation of *N*, *N*-dimethyl-2-methylpentylamine (**2-013**) (Scheme A-3)

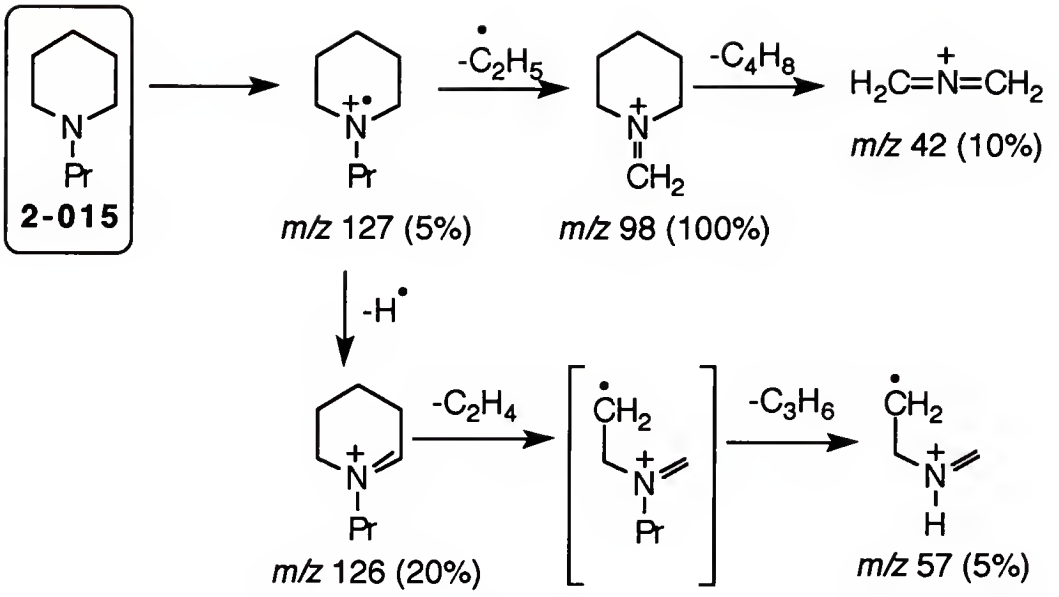
The major fragmentation of *N*,*N*-dimethyl-2-methylpentylamine (**2-013**) (Scheme A-3) (previously synthesized by Lukes and Pliml [50CCC512]) is an α-cleavage to give the ion corresponding to the base peak at *m/z* 58, with the simultaneous elimination of a *sec*-pentyl radical. As seen with all tertiary amines, and previously for *N*,*N*-dimethypentylamine (**2-009**), the largest alkyl group is lost preferentially [B-67MI298] The ion at *m/z* 100 (0.5%), is probably formed through γ-cleavage with the concomitant elimination of an ethyl radical. The ion at *m/z* 44 is a result of the loss of a methyl radical and a neutral C-5 fragment from the molecular ion, while the ion at *m/z* 113 resulted from loss of methane.



Scheme A-3

Fragmentation of 1-propylpiperidine (**2-015**) (Scheme A-4)

1-Propylpiperidine (**2-015**) (Scheme A-4) showed its molecular ion at *m/z* 127 (5%) and an α-cleavage gave the base peak at *m/z* 98 (100%), with the concomitant elimination of an ethyl radical. This is consistent with the fragmentation pattern of the other 1-alkylpiperidines (see Table 2-2 & 2-3, MS data for 1-methyl-, 1-ethyl-, 1-butyl- and 1-pentylpiperidine) which all undergo α-cleavage of the *N*-alkyl group to give the same base peak at *m/z* 98 [B-71MI371]. The fragments at *m/z* 57 and 42 are derived from further fragmentations of the piperidine ring and are again similar to the behavior of the 1-alkylpiperidines [B-71MI371]. In contrast, its 2-propylpiperidine isomer loses a propyl radical to give the base peak at *m/z* 84 [B-71MI368].



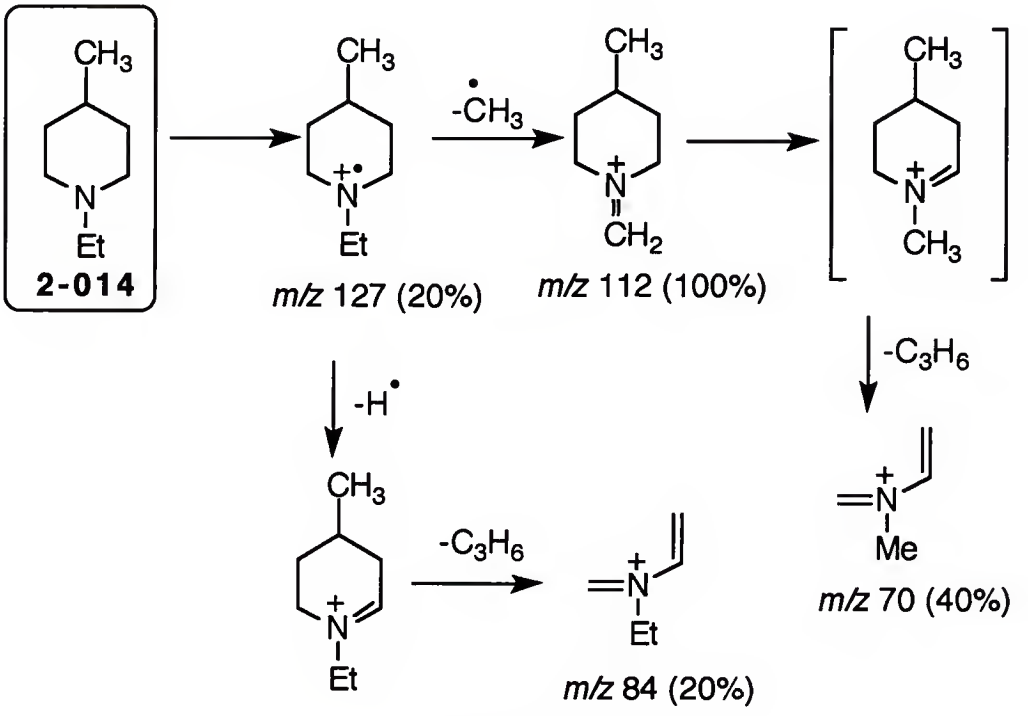
Scheme A-4

1-Alkyl-4-methylpiperidines (**2-014**, **2-016**, **2-018**, **2-025** and **2-028**) are easily identified from their fragmentation patterns which are similar to those of the corresponding 1-alkylpiperidines (**2-011**, **2-015**, **2-017**, **2-010** and **2-024**). The distinguishing factor is that the molecular ions and many of the fragmentations of the 1-alkyl-4-methylpiperidines differ from those of the 1-alkylpiperidines by 14 mass units. Each 1-alkyl-4-methylpiperidine showed its base peak at *m/z* 112, which is also 14 mass units higher than that for the 1-alkylpiperidines (*m/z* 98). This again conforms with the fragmentation patterns of 1-alkylpiperidines in which the 1-alkyl groups undergo α-cleavage to generate the base peak [B-71MI371] [see Table 2-2, MS data for 1,4-dimethylpiperidine (**2-010**)]. Common fragments at *m/z* 84, 70 and 44 confirm the presence of the piperidine moiety and further support the assigned structures.

Fragmentation of 1-ethyl-4-methylpiperidine (**2-014**) (Scheme A-5)

1-Ethyl-4-methylpiperidine (**2-014**) (Scheme A-5) showed the base peak at *m/z* 112. This is consistent with the fragmentation pattern of 1-alkylpiperidines in which the 1-

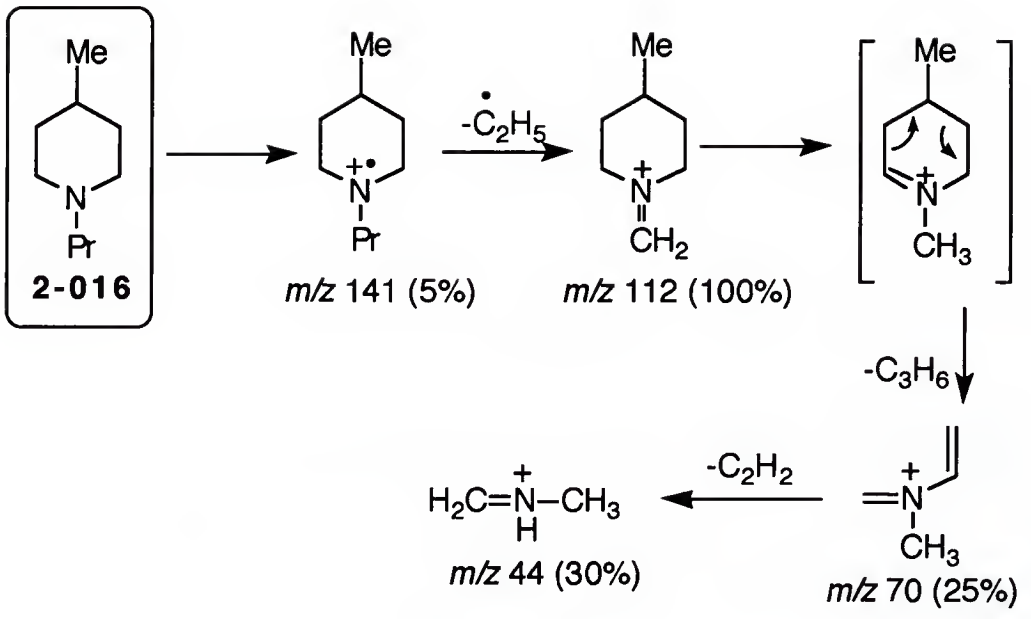
alkyl groups normally undergo α-cleavage to produce the base peak [B-71MI371] [see Table 2-2, MS for 1,4-dimethylpiperidine (**2-010**)]. The fragments at *m/z* 84 and 70 are a result of retro-Diels-Alder reactions [B-71MI371, 65JA810] which confirm the presence of the piperidine moiety and supports the assigned structure.



Scheme A-5

Fragmentation of 1-propyl-4-methylpiperidine (**2-016**) (Scheme A-6)

1-Propyl-4-methylpiperidine (**2-016**) (Scheme A-6) is easily identified from its fragmentation pattern, which is similar to that of 1-propylpiperidine (our compound **2-015**, Scheme A-4 above). The molecular ion at *m/z* 141 is now 14 mass units higher than that of 1-propylpiperidine. Compound **2-016** showed its base peak at *m/z* 112. The other fragments at *m/z* 70 (25%) and 44 (30%) confirm the presence of the piperidine moiety and further support the assigned structure.



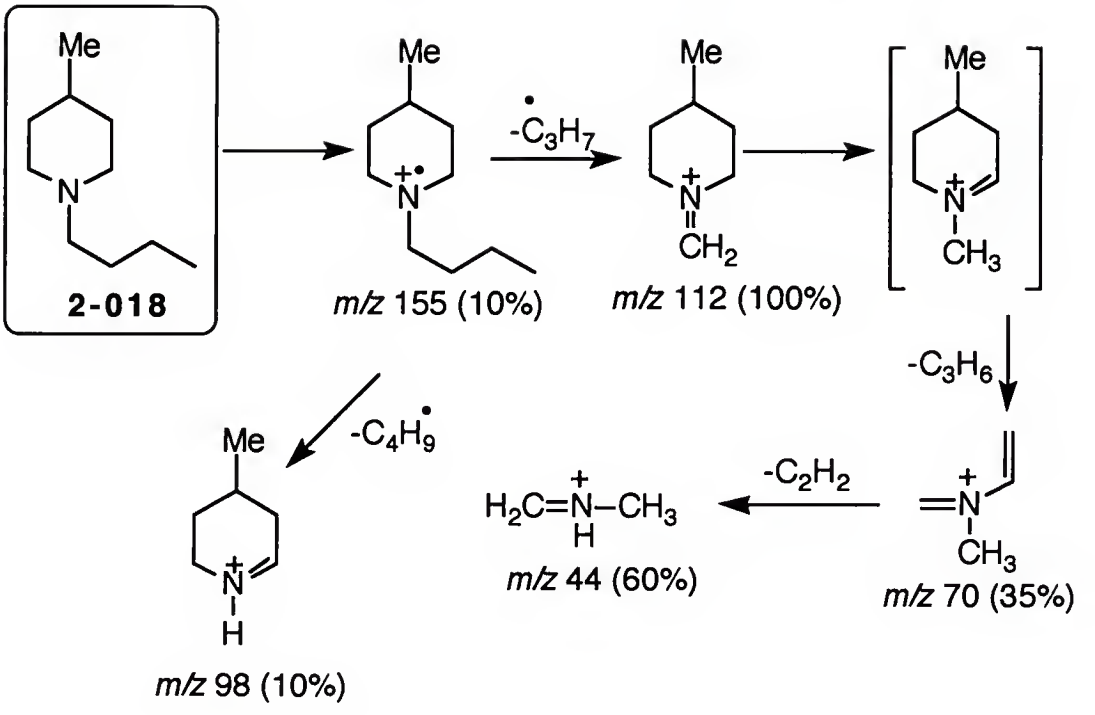
Scheme A-6

Fragmentation of 1-butyl-4-methylpiperidine (**2-018**) (Scheme A-7)

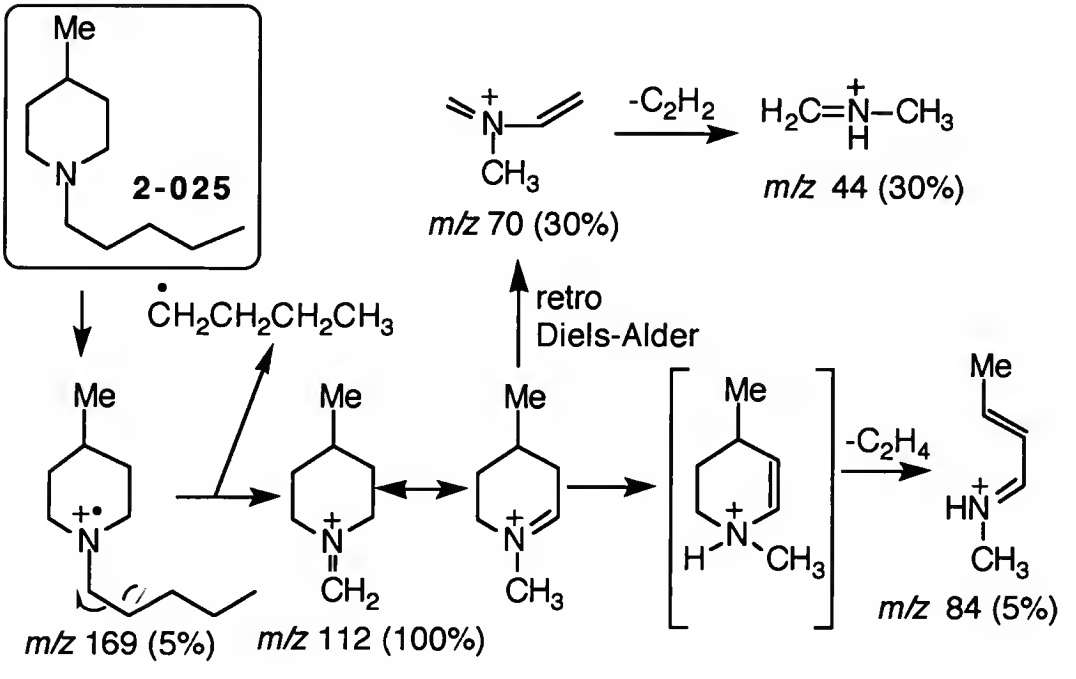
1-Butyl-4-methylpiperidine (**2-018**) (Scheme A-7) showed its molecular ion at *m/z* 155 (10%). Once again, the base peak appeared at *m/z* 112 as seen previously for compounds **2-014** and **2-016** (see Schemes A-5 & A-6). Other fragments at *m/z* 70 (35%) and 44 (60%) are derived from the piperidine moiety.

Fragmentation of 1-pentyl-4-methylpiperidine (**2-025**) (Scheme A-8)

1-Pentyl-4-methylpiperidine (**2-025**) (Scheme A-8) displays its molecular ion at *m/z* 169 (5%) and its base peak at *m/z* 112 as a result of the loss of the secondary alkyl radical. Compound **2-025** was obtained from the 4-methypiperidine run, and the mass difference between products **2-020** and **2-025** is 14 units. This result clearly suggests that **2-025** is a 1-alkyl-4-methylpiperidine. The base peak at *m/z* 112 supports the fragmentation of 1-alkylpiperidines in which the 1-alkyl group undergoes α-cleavage [B-73MI371]. As seen previously, fragments of *m/z* 70, and 44 are derived from the piperidine moiety.



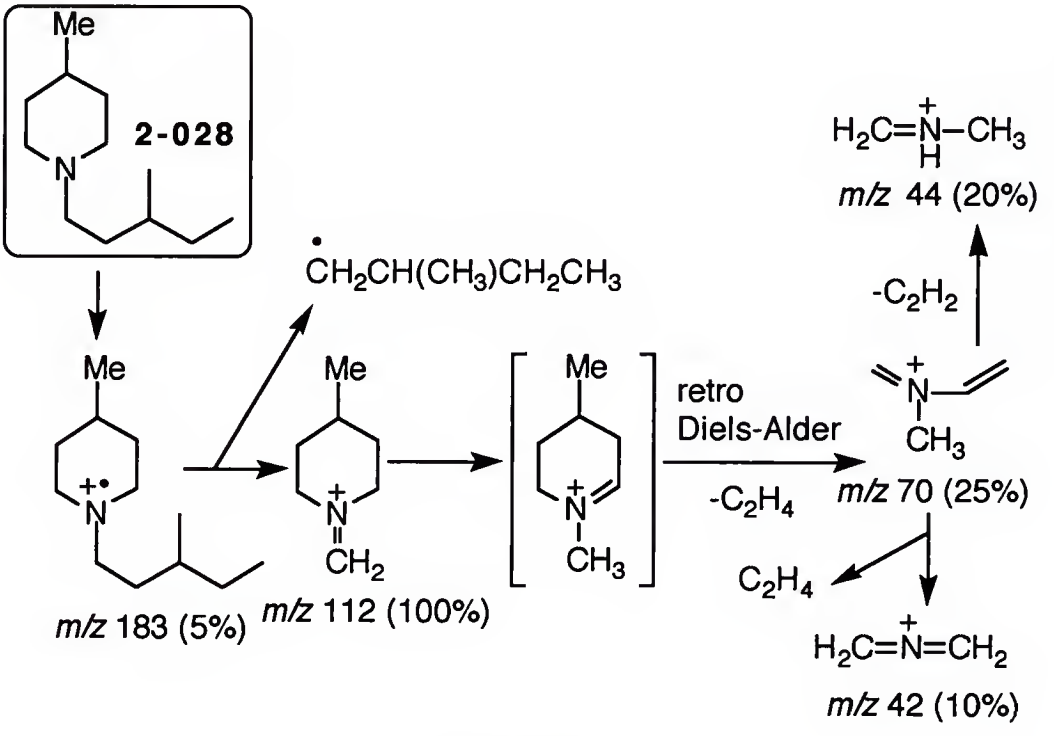
Scheme A-7



Scheme A-8

Fragmentation of 1-(3-methylpentyl)-4-methylpiperidine (**2-028**) (Scheme A-9)

1-(3-Methylpentyl)-4-methylpiperidine (**2-028**) (Scheme A-9) is obtained only from the 4-methylpyridine run. It displays its molecular ion at *m/z* 183 (5%). The base peak appears at *m/z* 112 (100%) as a result of α-cleavage of the alkyl chain. This suggests that product **2-028** should be a 1-alkyl-4-methylpiperidine. Fragments at *m/z* 70 and 44 are derived from the piperidine moiety as seen previously. Product **2-028** differs from its molecular ion at *m/z* 112 by 71 mass units. Based on the proposed mechanism for the formation of product **2-028** from the starting material, 4-methylpyridine, we suggest that the alkyl unit attached to the nitrogen is probably a 3-methylpentyl group.



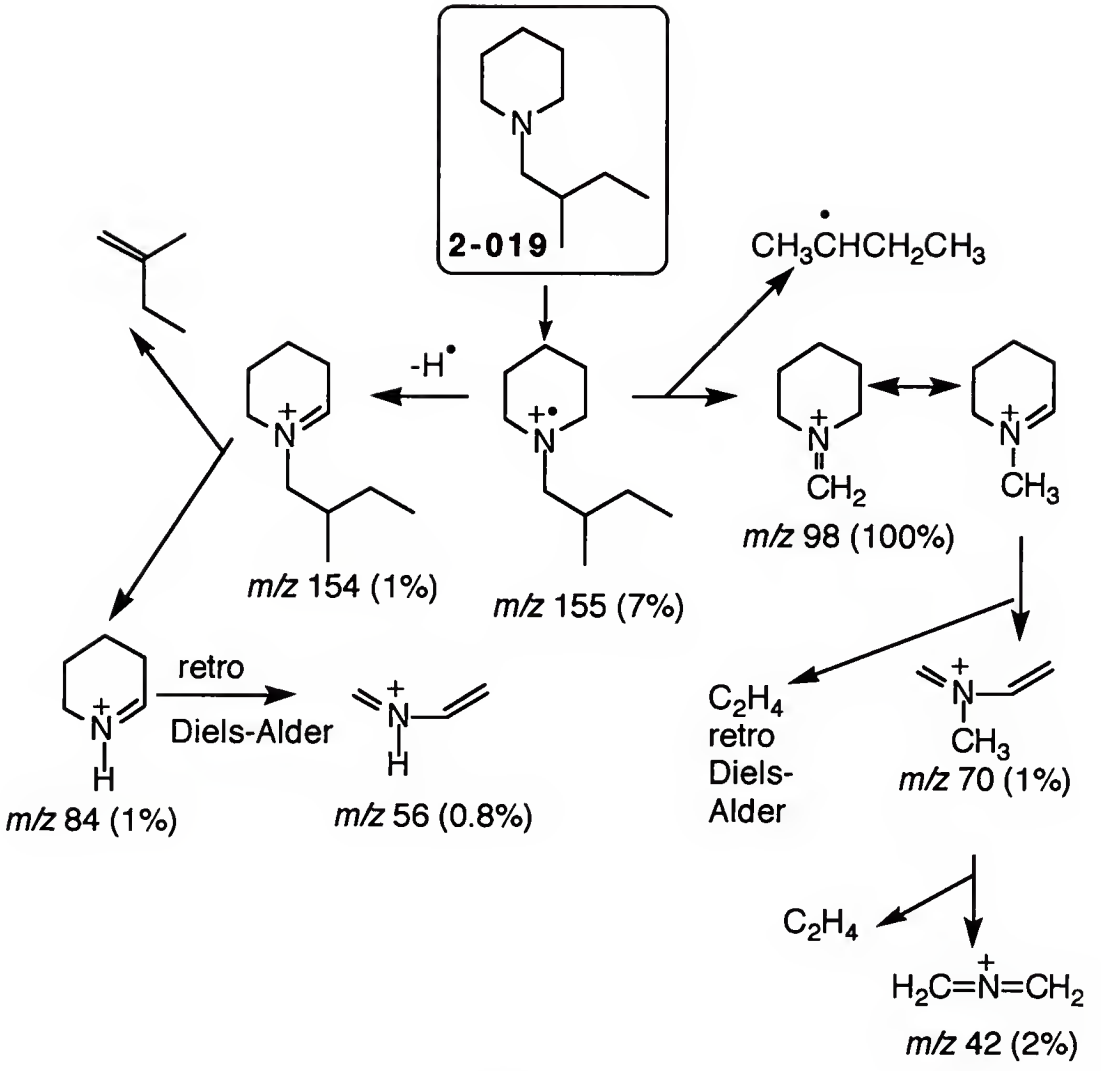
Scheme A-9

Fragmentation of 1-(2-methylbutyl)piperidine (**2-019**) (Scheme A-10)

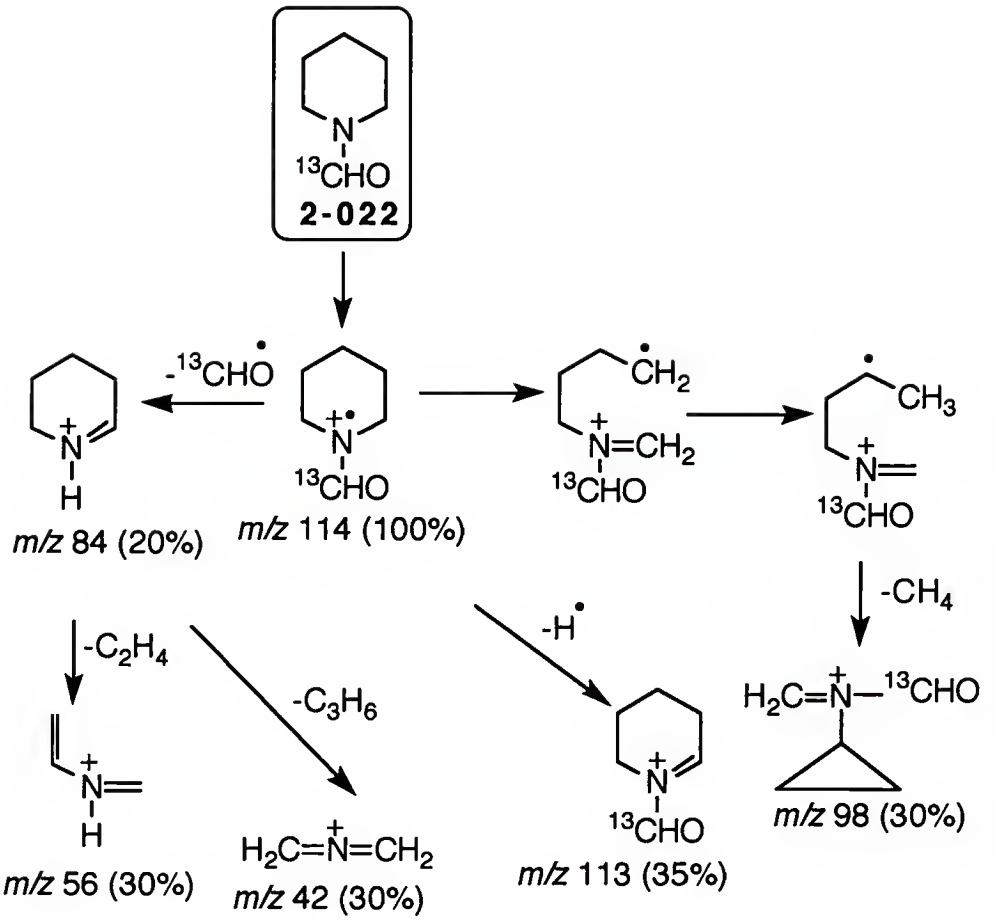
The novel compound 1-(2-methylbutyl)piperidine (**2-019**) (Scheme A-10) shows a molecular ion at *m/z* 155 (7%) and undergoes an α-cleavage to give its base peak at *m/z* 98 (100%), with the concomitant elimination of the *sec*-butyl radical. The base peak readily undergoes a 1,3-hydrogen shift to give an intermediate species, possessing the more stabilized endocyclic double bond. This intermediate species can undergo a retro-Diels-Alder reaction with the elimination of ethene to give the 2-azoniodiene cation. This is in line with the fragmentation of piperidine [B-85MI504]. The ion at *m/z* 70 can eliminate ethene to give the ion of *m/z* 42. Both these ions are found to be significant peaks in the mass spectrum of piperidine [B-85MI504, 64MI101] The molecular ion can also lose a hydrogen radical to give the ion at *m/z* 154 which can then eliminate a C-5 neutral with subsequent hydrogen rearrangement to give the ion of *m/z* 84. This ion can undergo a retro-Diels-Alder type process to give the azoniodiene ion at *m/z* 56.

Fragmentation of 1-(^{13}C)-formylpiperidine (**2-022**) (Scheme A-11)

1-(^{13}C)-Formylpiperidine (**2-022**) (Scheme A-11) has the same retention time as 1-formylpiperidine (**2-023**) and a fragmentation pattern which is identical to that of **2-023** except that the fragments containing the CHO group are 1 mass unit higher. Thus, it shows its molecular ion at *m/z* 114 as the base peak. Loss of a hydrogen atom from the molecular ion gives the ion at *m/z* 113 (35%). The fragmentation pattern was compared with the unlabeled 1-formylpiperidine. The fragment ion at *m/z* 84 (20%) is due to the loss of a CHO radical from the molecular ion. Further fragmentation generates the ions at *m/z* 56 (20%) and 42 (30%) which are derived from the piperidine moiety as shown previously for the other substituted piperidines.


2-019
CH3CHCH2CH3
-H•
m/z 154 (1%)
m/z 155 (7%)
CH2
CH3
m/z 98 (100%)
retro
Diels-Alder
m/z 84 (1%)
m/z 56 (0.8%)
C2H4
retro
Diels-
Alder
CH3
m/z 70 (1%)
C2H4
H2C=N=CH2
m/z 42 (2%)

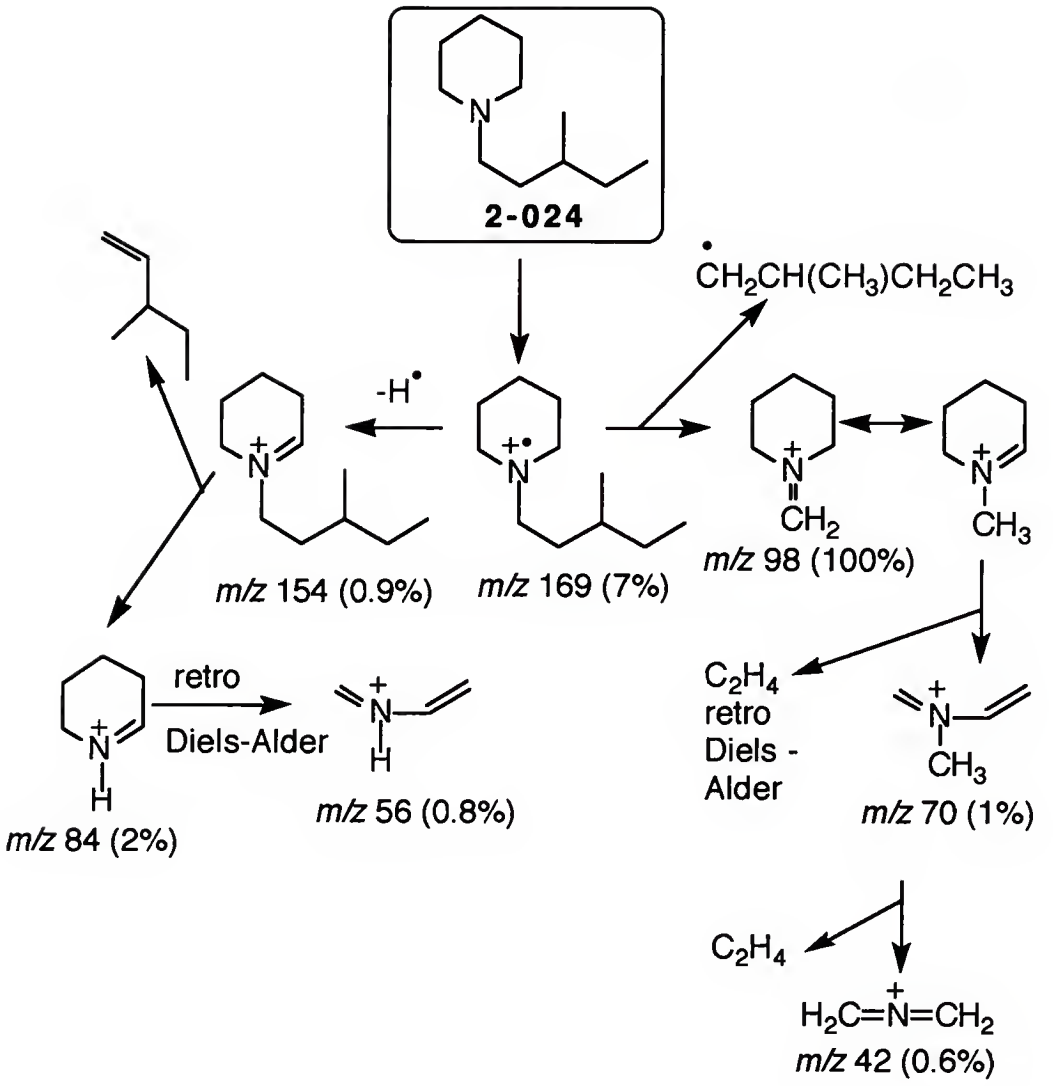
Scheme A-10



Scheme A-11

Fragmentation of 1-(3-methylpentyl)piperidine (**2-024**) (Scheme A-12)

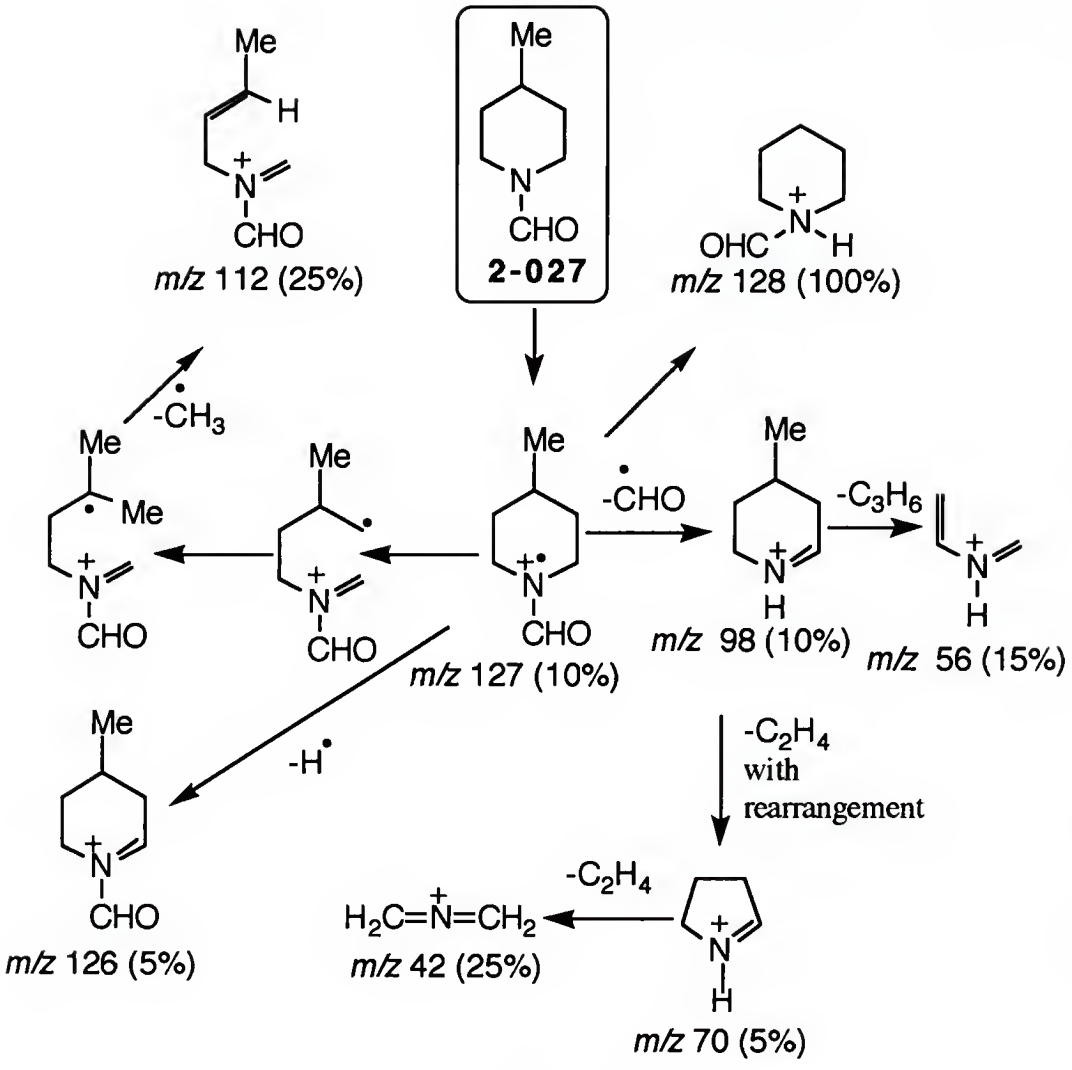
1-(3-Methylpentyl)piperidine (**2-024**) (Scheme A-12), a novel cyclic amine, shows a molecular ion at *m/z* 169 (7%) and this readily undergoes an α-cleavage with the concomitant elimination of a 2-methylbutyl secondary radical to give the base peak at *m/z* 98 (100%). The base peak then undergoes a retro-Diels-Alder reaction to give the ions at *m/z* 70 and 42, as seen previously [B-85MI504]. The ion at *m/z* 84 (1.8%) arises as a result of the elimination of a 3-methylpentyl radical, with a subsequent hydrogen rearrangement. This ion probably undergoes a retro-Diels-Alder reaction to give the ion at *m/z* 56 (0.8%).



Scheme A-12

Fragmentation of 1-formyl-4-methylpiperidine (**2-027**) (Scheme A-13)

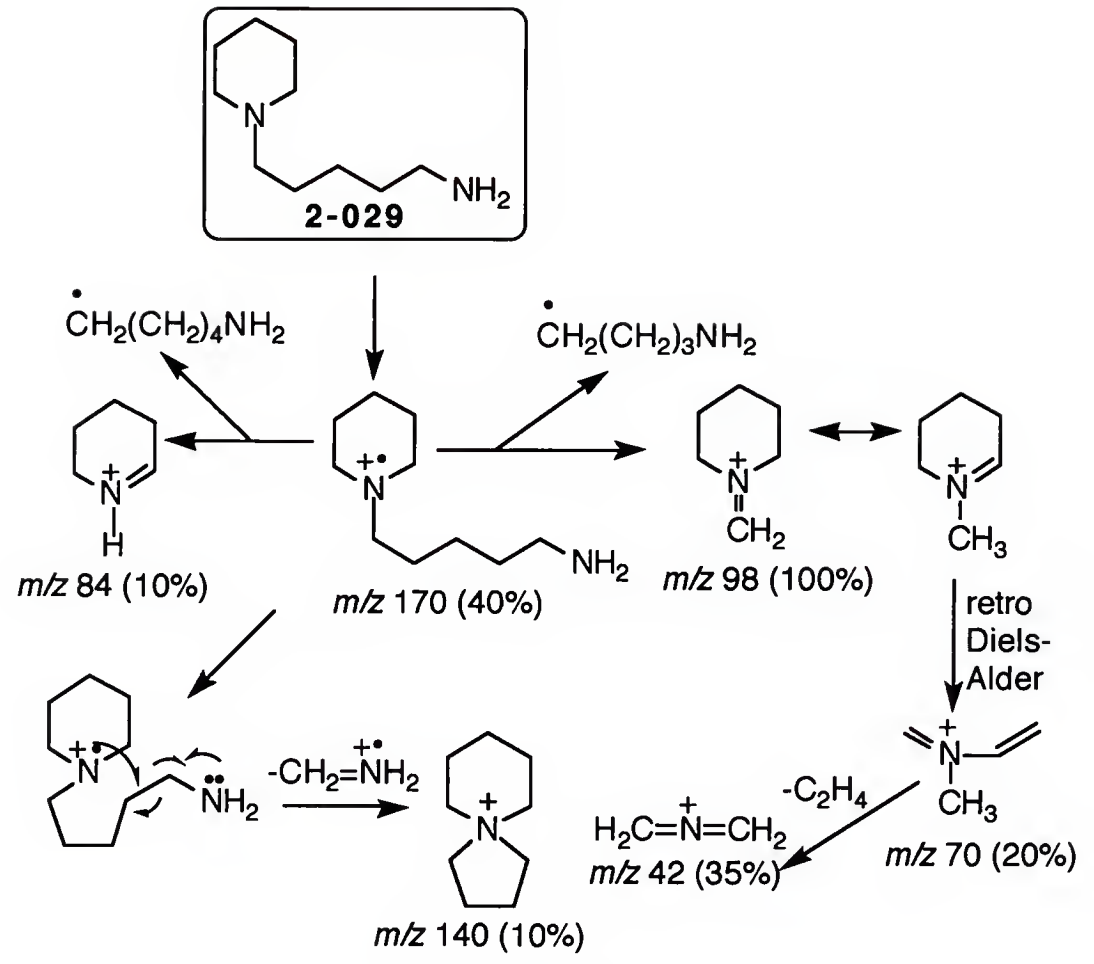
1-Formyl-4-methylpiperidine (**2-027**) (Scheme A-13) displays its molecular ion at *m/z* 127 (10%) and the base peak at *m/z* 128 (M^+1). The molecular ion loses H and CHO radicals to give fragment ions at *m/z* 126 (5%) and at *m/z* 98 (10%), respectively. Loss of a methyl radical from the molecular ion possibly by the pathway shown, gives the fragment ion at *m/z* 112 (25%). Other fragments at *m/z* 70 (5%), 56 (15%) and 42 (25%) are derived from the piperidine moiety by the routes indicated [66MI681].



Scheme A-13

Fragmentation of 1-(5-aminopentyl)piperidine (**2-029**) (Scheme A-14)

1-(5-Aminopentyl)piperidine (**2-029**) (Scheme A-14) shows its molecular ion at *m/z* 170 (40%). Loss of the aminopentyl radical from the molecular ion gives the base peak at *m/z* 98. This suggests that compound **2-029** is an *N*-substituted piperidine with an aminopentyl group as the *N*-substituent. Further fragments at *m/z* 70 (20%) and 42 (35%) are derived from the piperidine moiety. Together with that at *m/z* 140 (10%), they support the assigned structure of **2-029**.



Scheme A-14

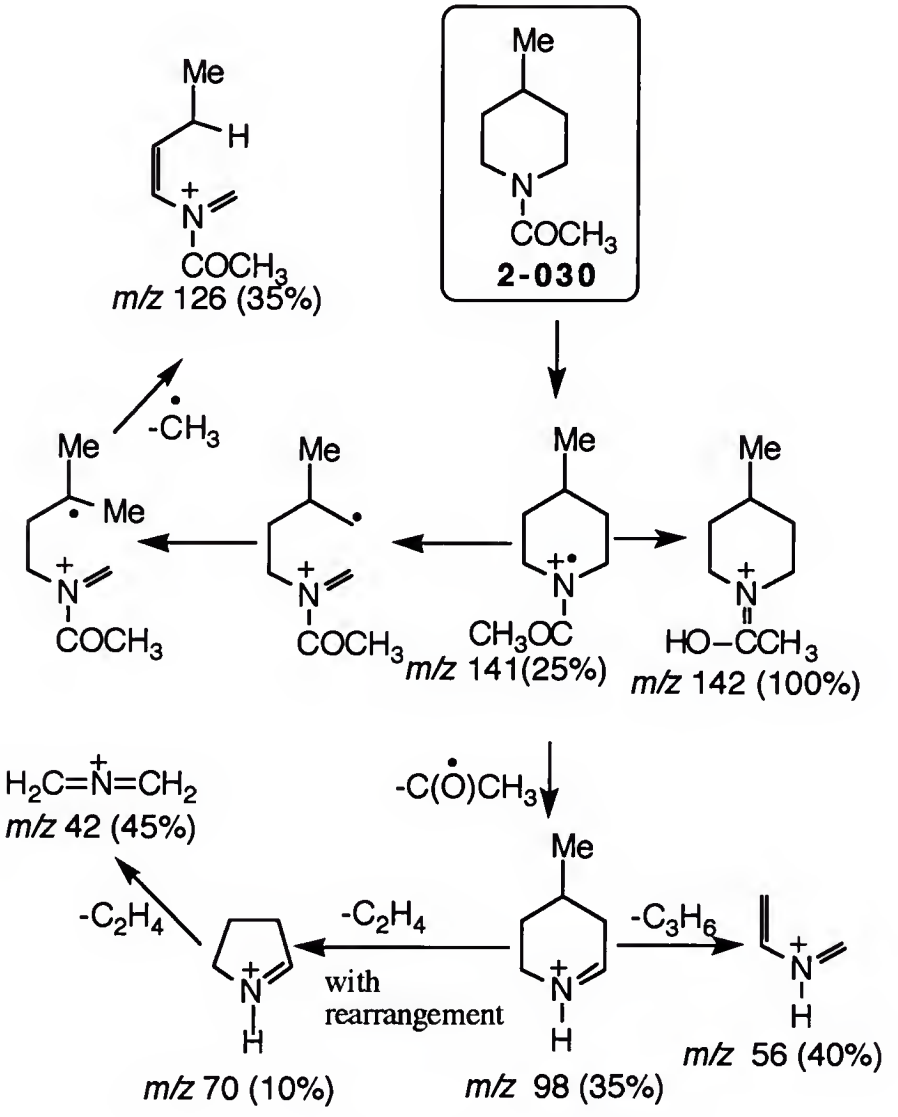
Fragmentation of 1-acetyl-4-methylpiperidine (**2-030**) (Scheme A-15)

1-Acetyl-4-methylpiperidine (**2-030**) (Scheme A-15) shows its molecular ion at *m/z* 141 (25%) and the base peak at *m/z* 142 (M^+1). Loss of a methyl radical and of an acetyl radical [B-85MI508] from the molecular ion give the fragment ions at *m/z* 126 (35%) and 98 (35%), respectively. Further fragmentation generates the ions at *m/z* 70 (10%), 56 (40%) and 42 (45%) which are derived from the piperidine moiety.

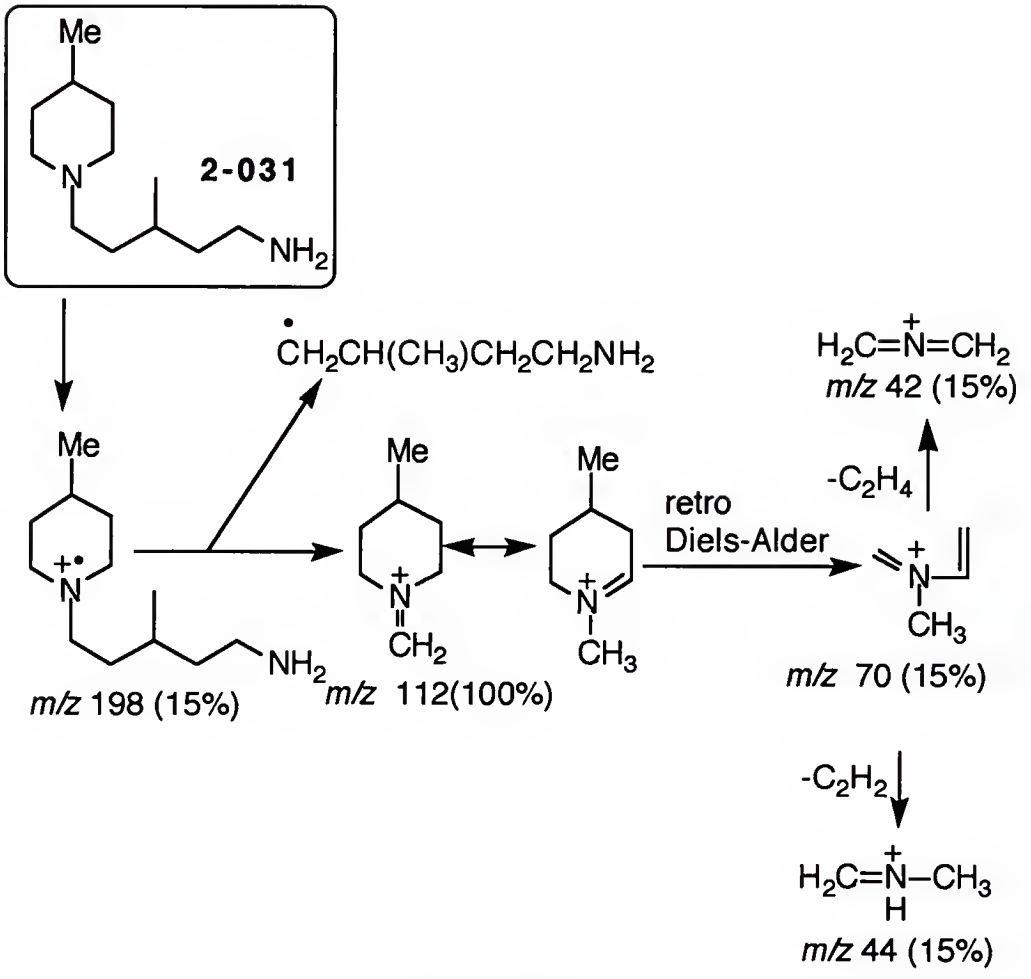
Fragmentation of 1-(3-methyl-5-aminopentyl)piperidine (**2-031**) (Scheme A-16)

1-(3-Methyl-5-aminopentyl)piperidine (**2-031**) (Scheme A-16) shows its molecular ion at *m/z* 198 (15%). The molecular ion loses the aminopentyl radical to give the base peak at *m/z* 112. The differences in the mass peaks of 4-methylpyridine or 4-

methylpiperidine (starting material) and product (**2-031**) suggests that it is an *N*-alkylated piperidine. The *N*-alkyl substituent is assigned the 3-methylpentylamine structure based largely on the proposed mechanism of formation. The other fragments at *m/z* 70 (15%), 44 (20%) and 42 (15%) are derived from the piperidine moiety and are in good agreement with the *N*-substituted-4-methyl piperidine structure assigned (Scheme A-16).



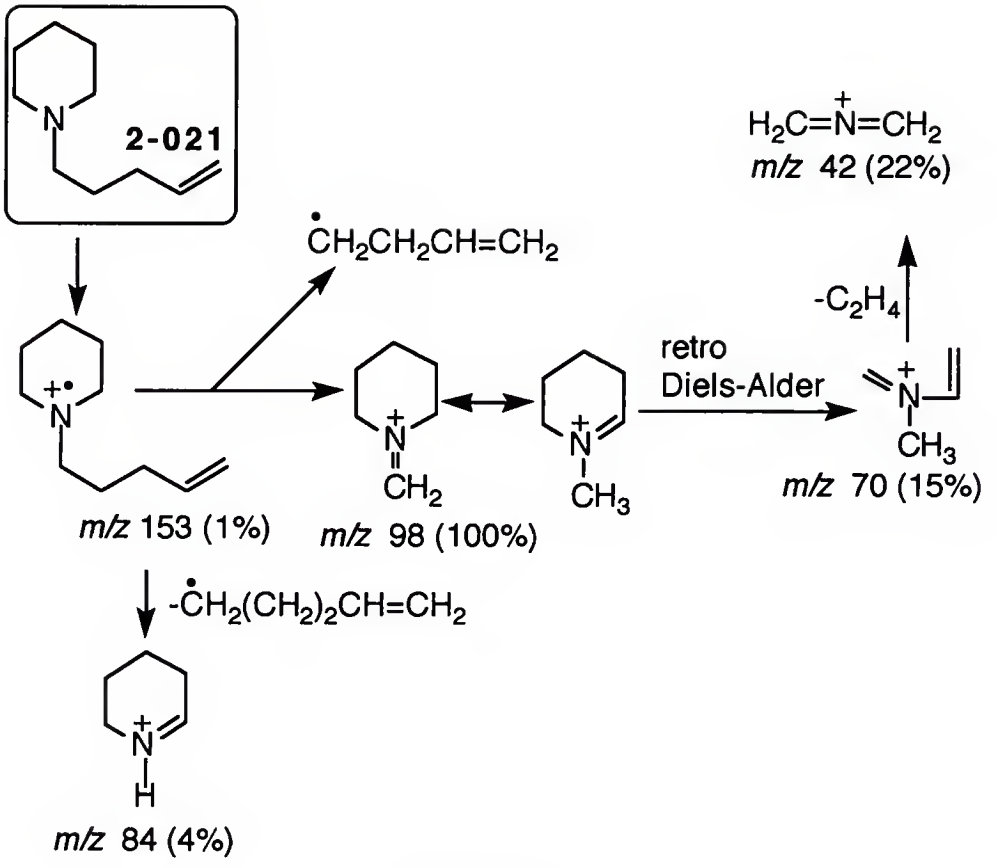
Scheme A-15



Scheme A-16

Fragmentation of 1-(pent-4-en-1-yl)piperidine (**2-021**) (Scheme A-17)

1-(Pent-4-en-1-yl)piperidine (**2-021**) (Scheme A-17) shows its molecular ion at *m/z* 153 (1%). The molecular ion loses the alkenyl radical to give the base peak at *m/z* 98. The differences in the mass peaks of 1-pentylpiperidine (**2-020**) and product **2-021** suggests that it is an unsaturated *N*-alkylated piperidine. The ion at *m/z* 84 (4%) arises from loss of the entire alkyl chain. The other fragments at *m/z* 70 (12%) and 42 (22%) are derived from the piperidine moiety and are in good agreement with the 1-(pent-4-en-1-yl)piperidine structure assigned.


2-021
$\dot{C}H_2CH_2CH=CH_2$
$H_2C=\overset{+}{N}=CH_2$
m/z 42 (22%)
-C_2H_4
retro
Diels-Alder
m/z 153 (1%)
m/z 98 (100%)
m/z 70 (15%)
-$\dot{C}H_2(CH_2)_2CH=CH_2$
m/z 84 (4%)

Scheme A-17

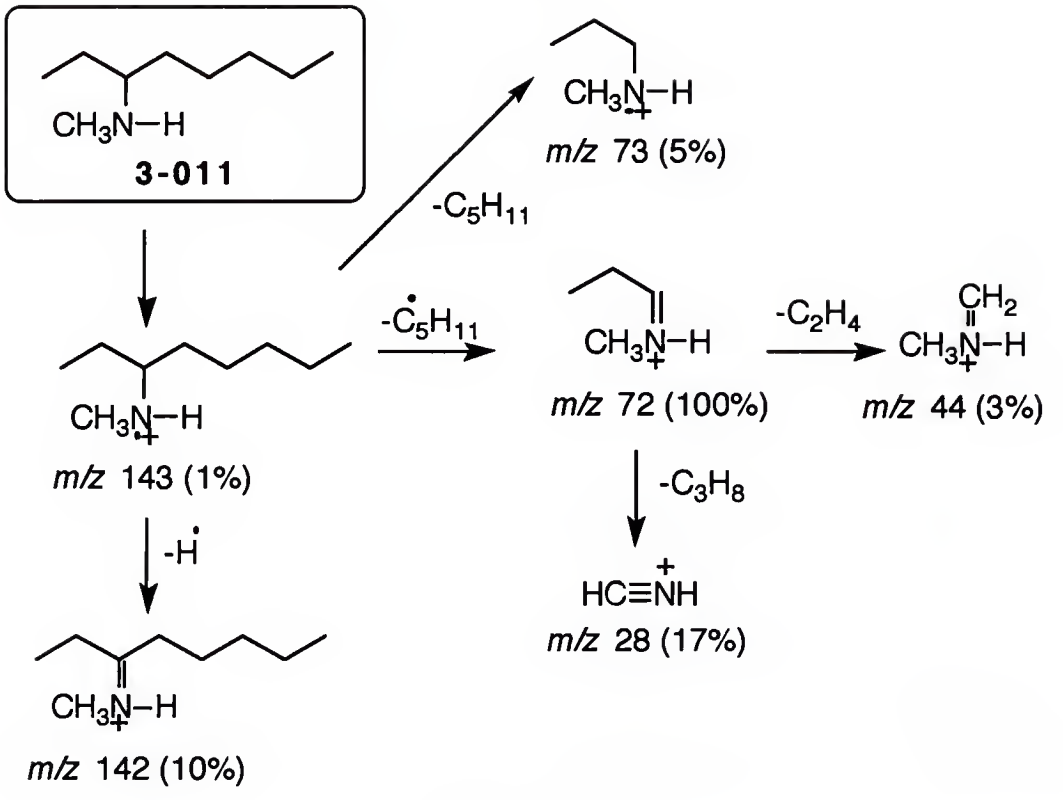
APPENDIX B
MASS SPECTRAL FRAGMENTATION PATTERNS OF ALIPHATIC PRODUCTS

Interpretation of mass spectral fragmentation patterns

Compounds identified in Chapter III, for which no published MS data was available were identified by analysis of their mass spectral fragmentation patterns, which are represented below. The products were assigned from their MS fragmentation patterns along with consideration of the reaction conditions and reasonable mechanistic pathways for their formation from the starting materials (see Table 3-4). In the following fragmentation schemes, fragment ions detected by GC/MS analyses are represented by mass units (*m/z*).

Fragmentation of *N*-methyl-3-octylamine (**3-011**) (Scheme B-1)

N-Methyl-3-octylamine (**3-011**) (Scheme B-1) displays its molecular ion at *m/z* 143 (1%). β-Cleavage of a pentyl radical generates the base at *m/z* 72 (100%). From the base peak, loss of ethylene leads to the ion at *m/z* 44 (3%), while loss of propane gives the ion at *m/z* 28 (17%). Other fragments from the molecular ion were *m/z* 142 (10%) through hydrogen radical loss and *m/z* 73 (5%) *via* loss of pentene.



Scheme B-1

Fragmentation of *N*-methyl-*N*-1-octylformamide (**3-024**) (Scheme B-2)

N-Methyl-*N*-1-octylformamide (**3-024**) (Scheme B-2) displays a weak molecular ion at *m/z* 171 (8%). α-Cleavage of a heptyl radical with subsequent hydrogen migration, generates the base peak at *m/z* 72 (100%). Loss of heptene from the molecular ion gives the ion *m/z* 73 (40%), which could lose CO to form the ion at *m/z* 45 (1%).

Cleavage of a methyl radical from the molecular ion gave the isocyanate ion at *m/z* 156 (7%). From this isocyanate ion α-cleavage of octene generates the ion at *m/z* 44 (42%), a characteristic peak of formamides [B-67MI336]. Alternatively, the ion at *m/z* 156 could eliminate CO to give the ion at *m/z* 128 (4%) which could then eliminate ethylene to give the ion at *m/z* 100 (9%).

The M^+-1 ion at *m/z* 170 was observed with a moderate intensity (11%). Loss of CO from this isocyanate ion gave the ion at *m/z* 142 (4%). Elimination of CO from the

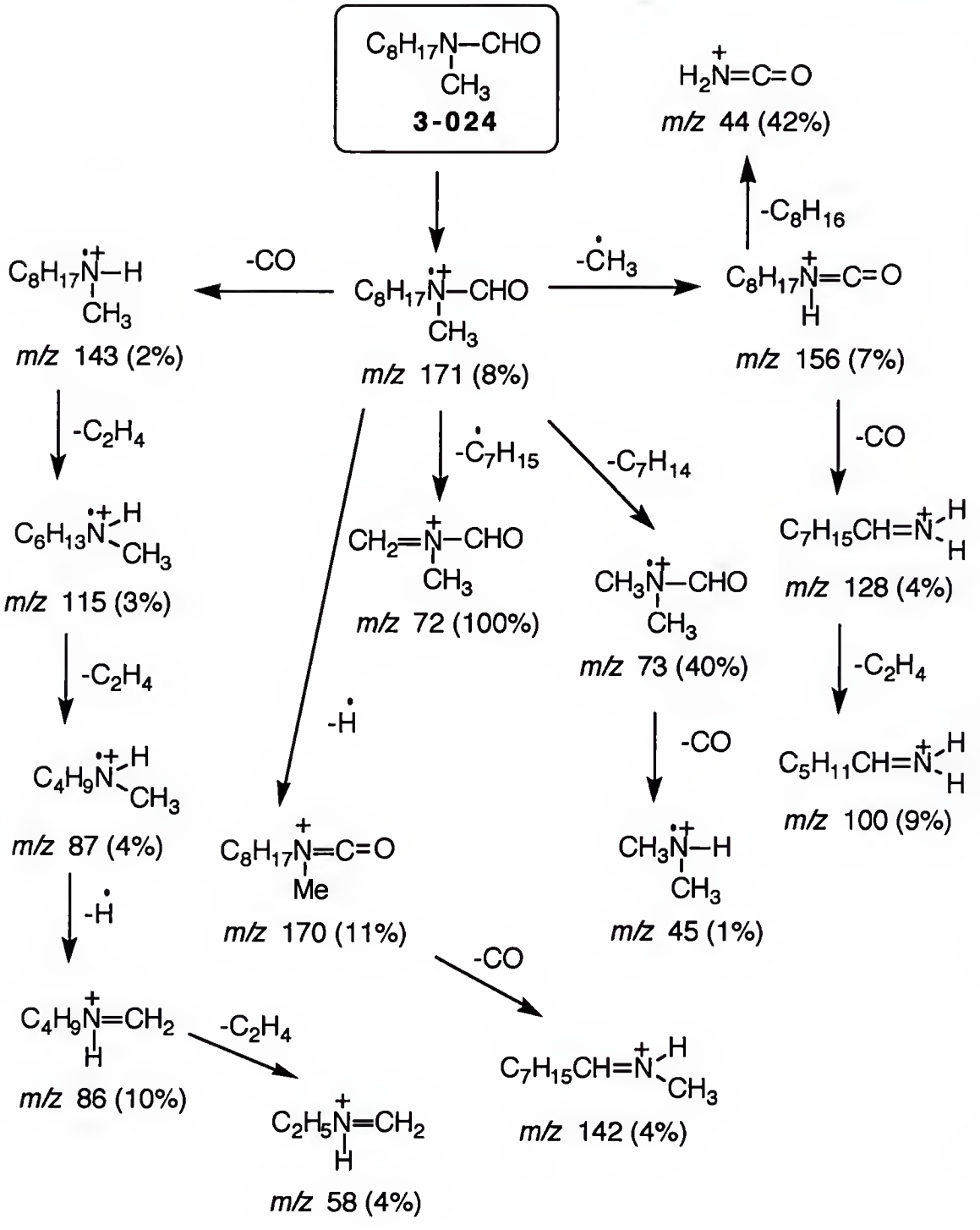
molecular ion gives the ion at *m/z* 143 (2%). From this ion, loss of ethylene gave the ion at *m/z* 115 (3%), which could also lose ethylene to give the ion at *m/z* 87 (4%). From this ion (*m/z* 87), hydrogen radical loss gave the ion at *m/z* 86 (10%), which could lose ethylene to form the ion at *m/z* 58 (4%) (Scheme B-2).

Fragmentation of *N*-1-octylacetamide (**3-025**) (Scheme B-3)

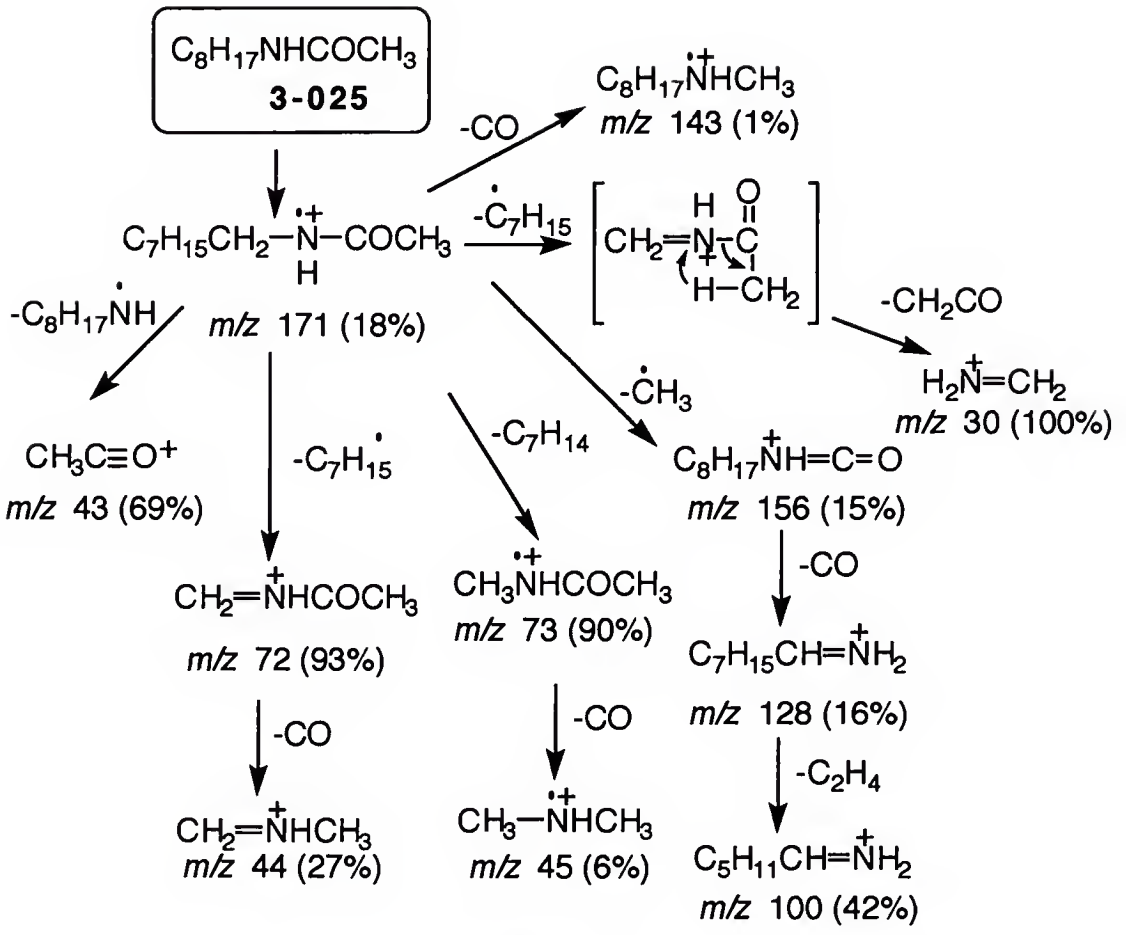
N-1-Octylacetamide (**3-025**) (Scheme B-3) displays its molecular ion at *m/z* 171 (18%) (moderate intensity normal for acetamides). Normally, secondary amides are characterized by double α- and C-N cleavage with hydrogen rearrangement [B-67MI336]. However, in the absence of α-substitution adjacent to the N, ions of mass 30 are formed by a similar fragmentation [B-67MI338]. Such is the case with formation of the base peak for *N*-octylacetamide. α-Cleavage of a heptyl radical could produce an intermediate ion which, upon elimination of CH_2=C=O, would lead to the base peak at *m/z* 30 (100%).

Loss of a methyl radical from the molecular ion gave the alkyl isocyanate ion at *m/z* 156 (15%). This isocyanate ion could then lose CO to form the ion at *m/z* 128 (3.25%). From this ion at *m/z* 128 loss of ethylene generated the ion at *m/z* 100 (42%).

The molecular ion could also lose a heptyl radical to form the acyl ion at *m/z* 72 (93%) which could lose CO to generate the ion at *m/z* 44 (27%). In contrast, loss of the heptene from the molecular ion generates the ion at *m/z* 73 (90%), which could further lose CO to form the ion at *m/z* 45 (6%). Loss of CO from the molecular ion leads the ion at *m/z* 143 at a weak intensity (1%) (Scheme B-3).


C8H17N–CHO
CH3
3-024
m/z 171 (8%)
-CO
C8H17N–H
CH3
m/z 143 (2%)
-CH3
H2N=C=O
m/z 44 (42%)
-C8H16
C8H17N=C=O
H
m/z 156 (7%)
-C2H4
C6H13N–H
CH3
m/z 115 (3%)
-C7H15
CH2=N–CHO
CH3
m/z 72 (100%)
-C7H14
CH3N–CHO
CH3
m/z 73 (40%)
-CO
C7H15CH=N–H
H
m/z 128 (4%)
-C2H4
C4H9N–H
CH3
m/z 87 (4%)
-H
C8H17N=C=O
Me
m/z 170 (11%)
-CO
CH3N–H
CH3
m/z 45 (1%)
-C2H4
C5H11CH=N–H
H
m/z 100 (9%)
-H
C4H9N=CH2
H
m/z 86 (10%)
-C2H4
C2H5N=CH2
H
m/z 58 (4%)
-CO
C7H15CH=N–H
CH3
m/z 142 (4%)

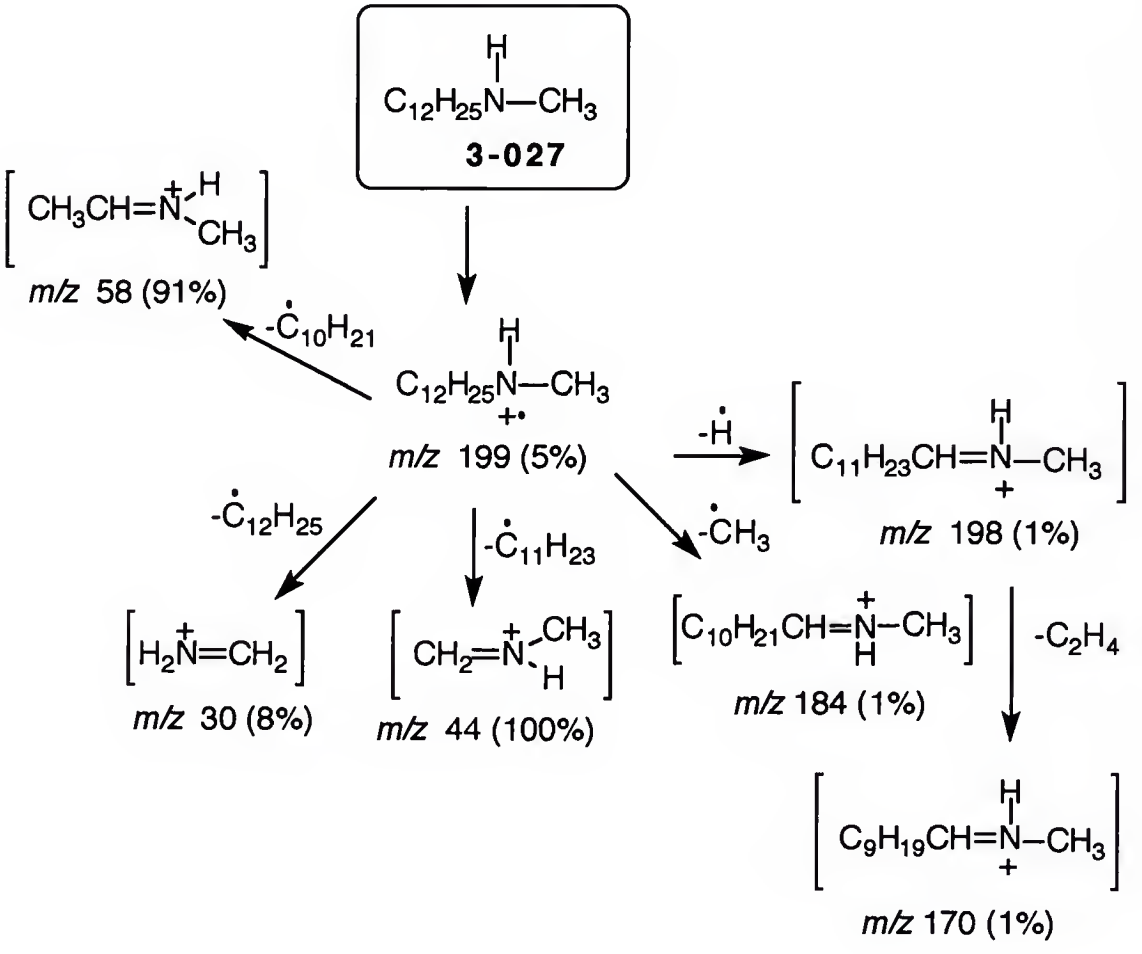
Scheme B-2


C8H17NHCOCH3
3-025
-CO
C8H17NHCH3
m/z 143 (1%)
C7H15CH2–N–COCH3
H
-C7H15
CH2=N–C
H–CH2
-C8H17NH
m/z 171 (18%)
-CH2CO
H2N=CH2
m/z 30 (100%)
-CH3
CH3C≡O+
m/z 43 (69%)
-C7H15
-C7H14
C8H17NH=C=O
m/z 156 (15%)
-CO
CH2=NHCOCH3
m/z 72 (93%)
CH3NHCOCH3
m/z 73 (90%)
C7H15CH=NH2
m/z 128 (16%)
-CO
-CO
-C2H4
CH2=NHCH3
m/z 44 (27%)
CH3–NHCH3
m/z 45 (6%)
C5H11CH=NH2
m/z 100 (42%)

Scheme B-3

Fragmentation of *N*-methyl-1-dodecylamine (**3-027**) (Scheme B-4)

N-Methyl-1-dodecylamine (**3-027**) (Scheme B-4) shows its molecular ion at *m/z* 199 (5%). α-Cleavage [B-67MI297] of an undecyl radical provides the base peak at *m/z* 44 (100%). Loss of a hydrogen radical from the molecular ion can generate the ion at *m/z* 198 (1%). Loss of an ethylene molecule from this ion at *m/z* 198 gives rise to the ion at *m/z* 170 (1%). Fragmentation by loss of a dodecyl radical from the molecular ion generates the ion at *m/z* 30 (8%). Loss of an *n*-decyl radical from the molecular ion forms the ion at *m/z* 58 (91%). Loss of a methyl radical from the molecular ion forms the ion at *m/z* 184 (1%).



Scheme B-4

Fragmentation of *N*-methyl-*N*-1-octylacetamide (**3-029**) (Scheme B-5)

N-Methyl-*N*-1-octylacetamide (**3-029**) (Scheme B-5) displays its molecular ion at *m/z* 185 (6%). α–Cleavage with elimination of a heptyl radical generated the base peak at *m/z* 86 (100%). From the base peak, loss of CO results in the ion at *m/z* 58 (36%).

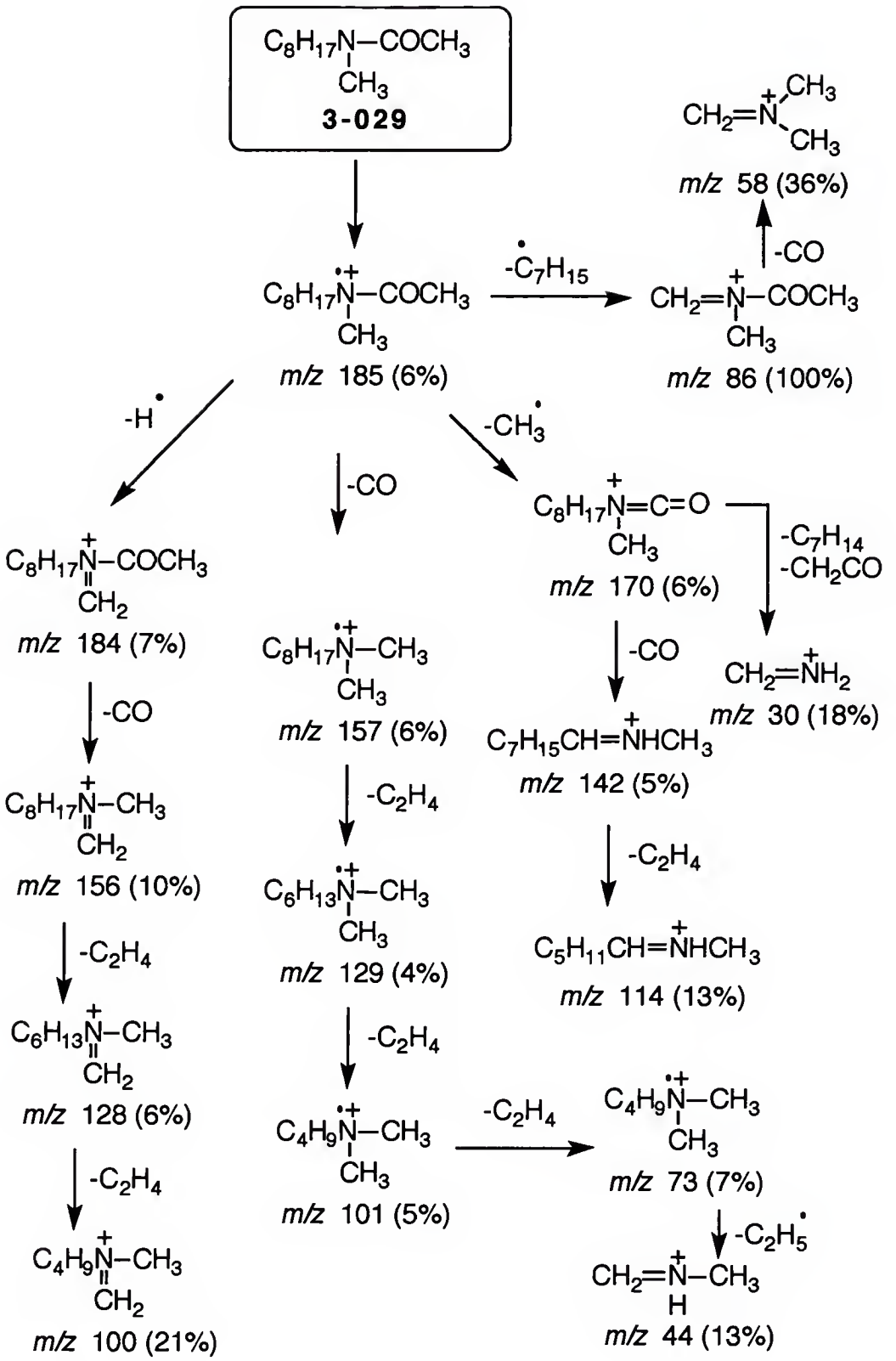
Hydrogen radical loss from the molecular ion gave the M^+-1 at *m/z* 184 (7%). Loss of CO from this ion could generate the ion at *m/z* 156 (10%) which could subsequently undergo sequential loss of ethylene (multiples of 28 mass units) to generate the ions at *m/z* 128 (6%) and *m/z* 100 (21%) as described previously.

Similarly, loss of CO from the molecular ion generates the ion at at *m/z* 157 (6%), which, through ethylene loss, could generate the following series of ions: *m/z* 129 (4%), 101 (5%) and 73 (7%). From the ion at *m/z* 73 loss of an ethyl radical gives the ion at *m/z* 44 (13%).

The molecular ion could alternatively lose a methyl radical to form the ion at *m/z* 170 (6%) which, as described previously, could undergo loss of CO and ethylene to form the ions at *m/z* 142 (5%) and 114 (13%). The observation of the ion at *m/z* 30 (18%) [B-67MI338] supports the acetamide structure proposed.

Fragmentation of *N*-acetyl-*N*-1-octylformamide (**3-030**) (Scheme B-6)

N-Acetyl-*N*-1-octylformamide (**3-030**) (Scheme B-6) displays its molecular ion at *m/z* 199 (3%). Two major fragmentation pathways have been noted. Firstly, loss of a hydrogen radical generates the ion at *m/z* 198 (2%) which can lose CO to yield the base peak at *m/z* 170 (100%). The base peak can fragment by loss of CO to yield the ion at *m/z* 142 (3%) followed by sequential loss of ethylene to generate the ions at *m/z* 114 (11%), 86 (6%), 58 (11%) and 30 (13%). Loss of molecular hydrogen from the ion at *m/z* 30 may lead to the ion at *m/z* 28 (25%).

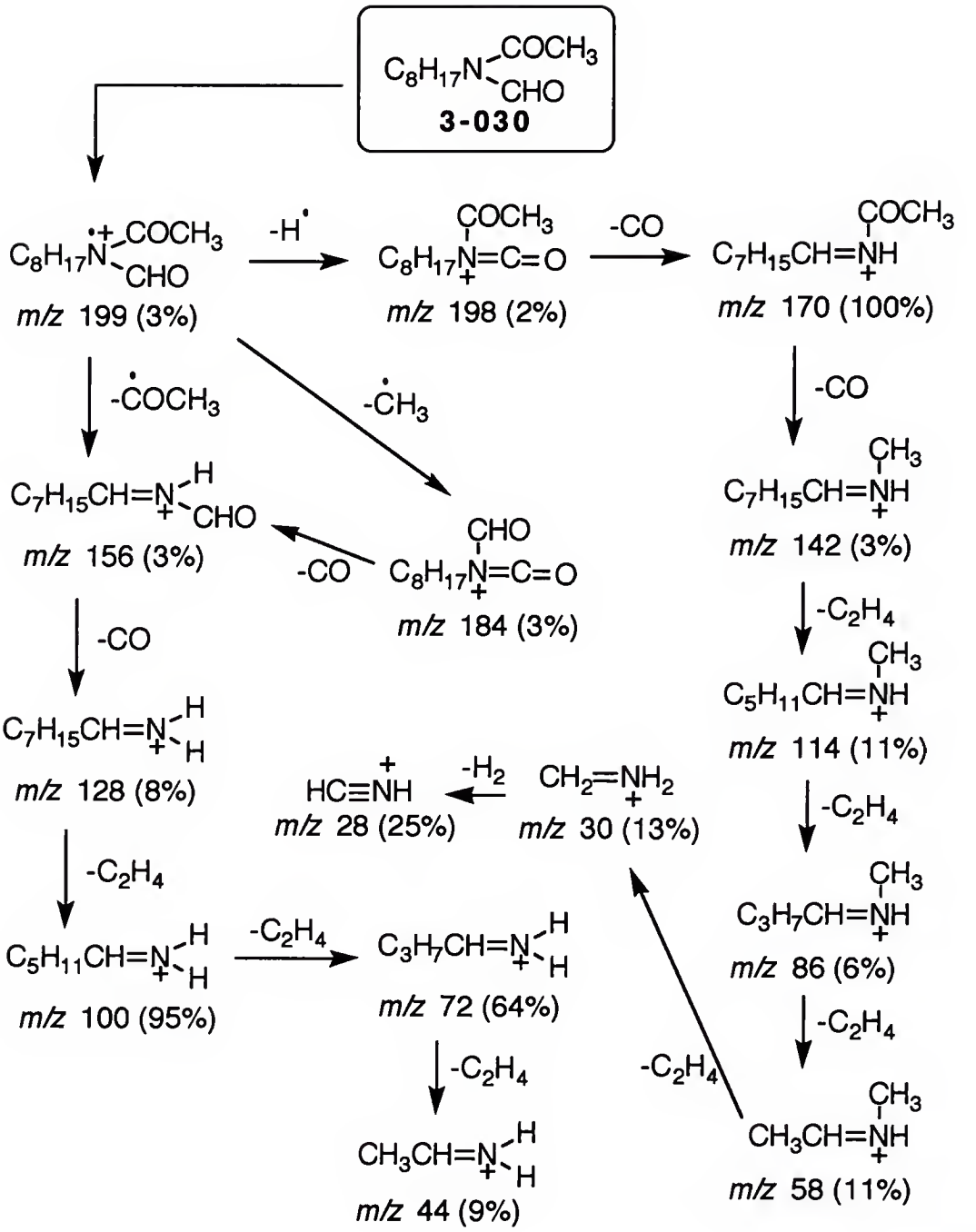

C8H17N–COCH3
CH3
3-029
C8H17N+•–COCH3
CH3
m/z 185 (6%)
-•C7H15
CH2=N+–COCH3
CH3
m/z 86 (100%)
CH2=N+(CH3)2
m/z 58 (36%)
-CO
-H•
-CH3•
-CO
C8H17N+=C=O
CH3
m/z 170 (6%)
-C7H14
-CH2CO
CH2=NH2+
m/z 30 (18%)
C8H17N+–COCH3
CH2
m/z 184 (7%)
C8H17N+•–CH3
CH3
m/z 157 (6%)
-CO
C7H15CH=NHCH3+
m/z 142 (5%)
-CO
C8H17N+–CH3
CH2
m/z 156 (10%)
-C2H4
-C2H4
C6H13N+•–CH3
CH3
m/z 129 (4%)
-C2H4
C5H11CH=NHCH3+
m/z 114 (13%)
-C2H4
C6H13N+–CH3
CH2
m/z 128 (6%)
-C2H4
C4H9N+•–CH3
CH3
m/z 101 (5%)
-C2H4
C4H9N+•–CH3
CH3
m/z 73 (7%)
-C2H5•
C4H9N+–CH3
CH2
m/z 100 (21%)
CH2=N+–CH3
H
m/z 44 (13%)

Scheme B-5

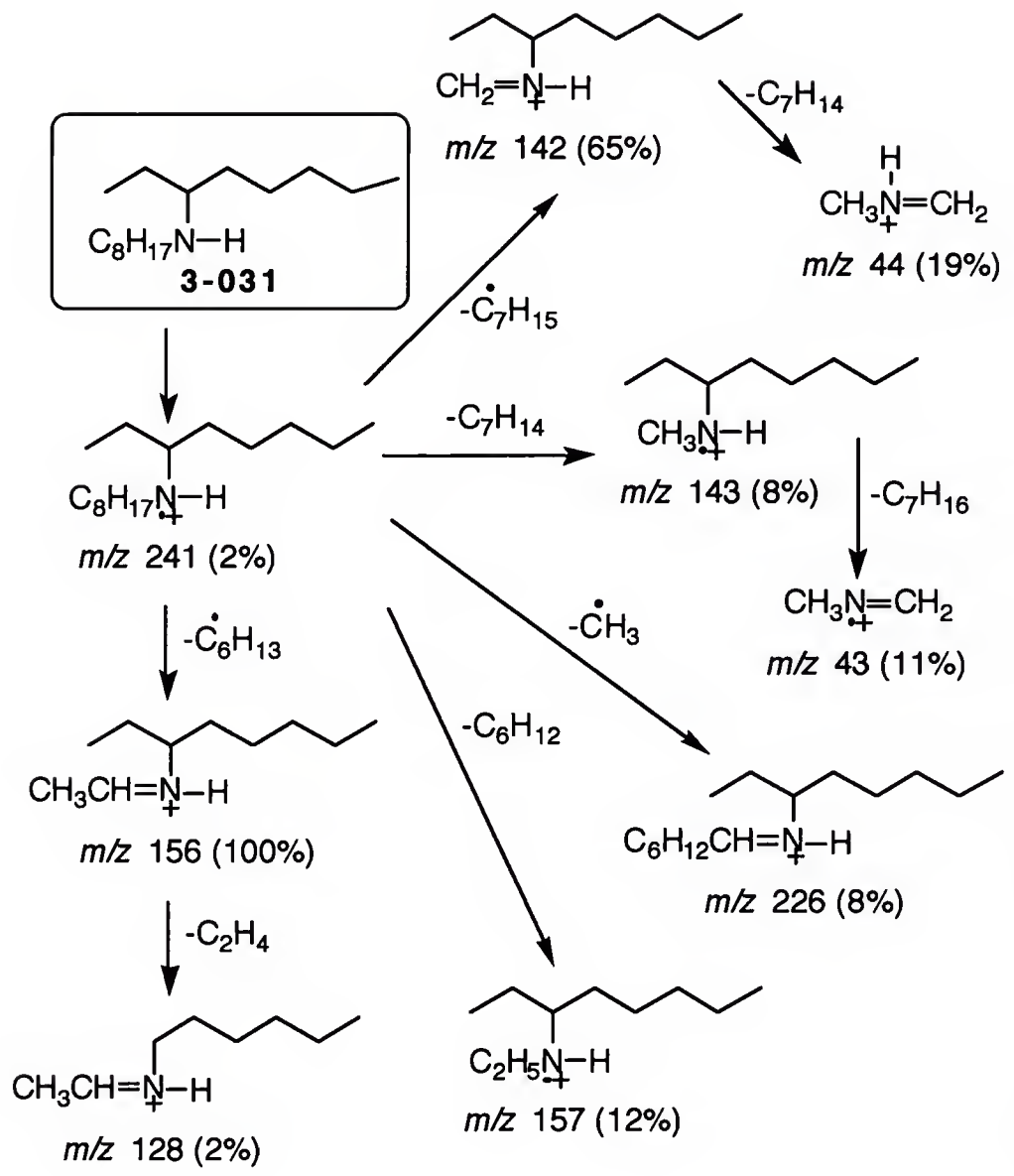
The other likely major fragmentation pathway involves initial loss of a methyl radical from the molecular ion to yield the ion at *m/z* 184 (3%) followed by sequential loss of two molecules of CO to generate ions at *m/z* 156 (3%) and 128 (8%), respectively. Further fragmentation from *m/z* 128 by sequential loss of ethylene can generate the ions observed at *m/z* 100 (95%), 72 (64%) and 44 (9%). Alternatively, the ion at *m/z* 156 may be formed through loss of an acetyl radical from the molecular ion (Scheme B-6).

Fragmentation of *N*-1-octyl-*N*-3-octylamine (**3-031**) (Scheme B-7)

N-1-Octyl-*N*-3-octylamine (**3-031**) (Scheme B-7) displays its molecular ion at *m/z* 241 (2%). β-Cleavage of a hexyl radical generates the base peak at *m/z* 156 (100%). From the base peak, loss of ethylene leads to the ion at *m/z* 128 (2%). Radical losses from the molecular ion include: methyl radical loss to give the ion at *m/z* 226 (8%) and loss of a heptyl radical leads to the ion at *m/z* 142 (65%). From the ion at *m/z* 142 loss of heptene generates the ion at *m/z* 44 (19%). Similarly, loss of heptene from the molecular ion (*via* a rearrangement) leads to the ion at *m/z* 143 (8%), from which loss of heptane can lead to the ion at *m/z* 43 (11%). Also, loss of hexene from the molecular ion leads to the ion at *m/z* 157 (12%).


C8H17N(COCH3)CHO
3-030
m/z 199 (3%)
-H•
m/z 198 (2%)
-CO
m/z 170 (100%)
-•COCH3
-•CH3
m/z 156 (3%)
-CO
m/z 184 (3%)
-CO
m/z 142 (3%)
-C2H4
m/z 114 (11%)
-C2H4
m/z 128 (8%)
-CO
-H2
m/z 28 (25%)
m/z 30 (13%)
-C2H4
m/z 86 (6%)
-C2H4
m/z 100 (95%)
-C2H4
m/z 72 (64%)
-C2H4
-C2H4
m/z 58 (11%)
m/z 44 (9%)

Scheme B-6



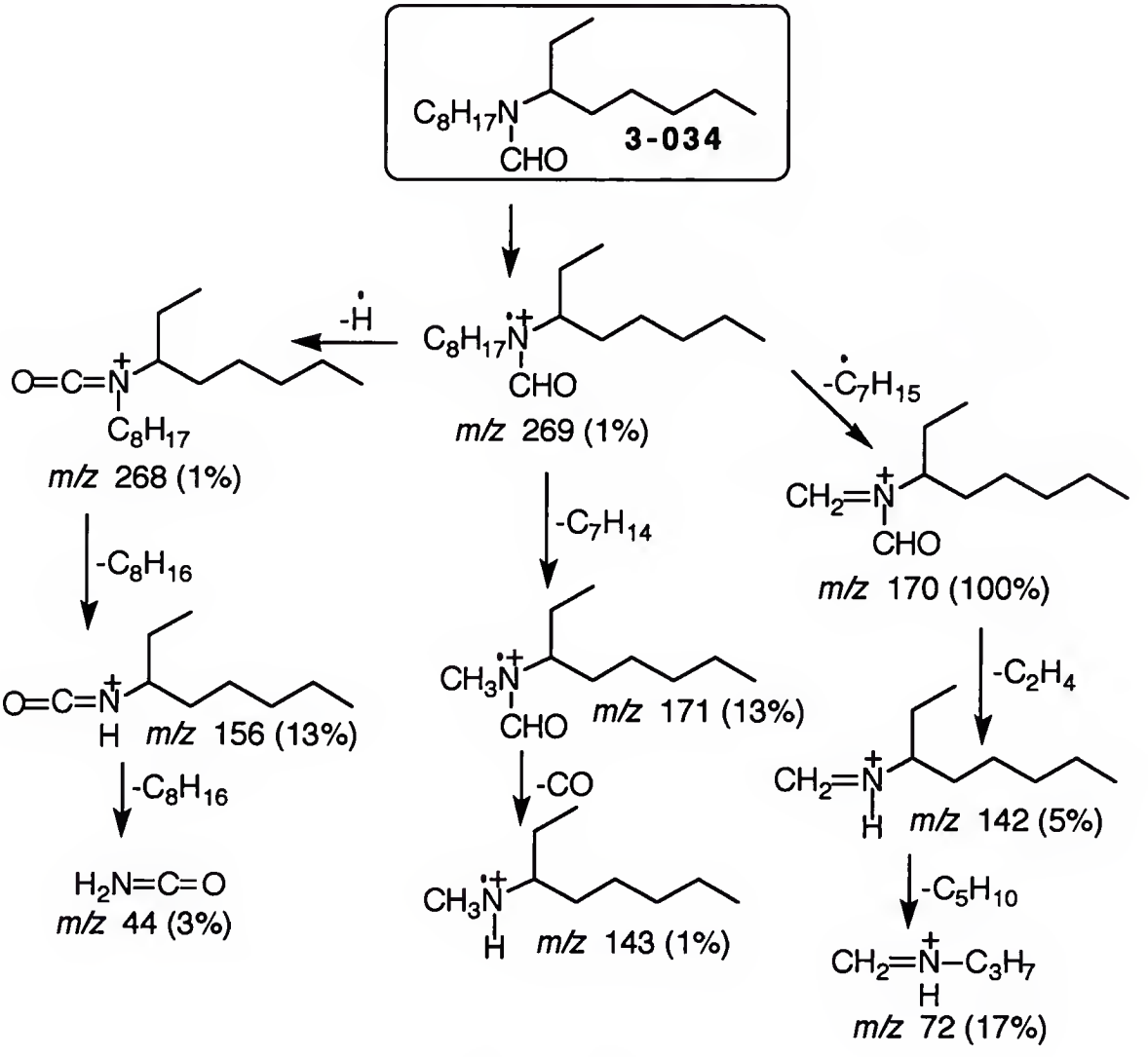
Scheme B-7

Fragmentation of *N*-1-octyl-*N*-3-octylformamide (**3-034**) (Scheme B-8)

N-1-Octyl-*N*-3-octylformamide (**3-034**) (Scheme B-8) displays its molecular ion at *m/z* 269 (1%). α-Cleavage of a heptyl radical generates the base peak at *m/z* 170 (100%).

From this ion (*m/z* 170) loss of CO leads to the ion at *m/z* 142 (5%). A subsequent loss of pentene forms the ion at *m/z* 72 (17%).

The M^+-1 ion (*m/z* 268) was observed at a very low intensity (1%). Loss of an octene molecule from the M^+-1 ion generated the ion at *m/z* 156 (13%) and subsequent loss of another octene molecule results in the ion at *m/z* 44 (3%). An alternative α-cleavage of heptene from the molecular ion gives the ion at *m/z* 171 (13%) and subsequent loss of CO results in the minor ion at *m/z* 143 (1%) (Scheme B-8).



Scheme B-8

Fragmentation of *N*-methyl-*N*-1-dodecylformamide (**3-036**) (Scheme B-9)

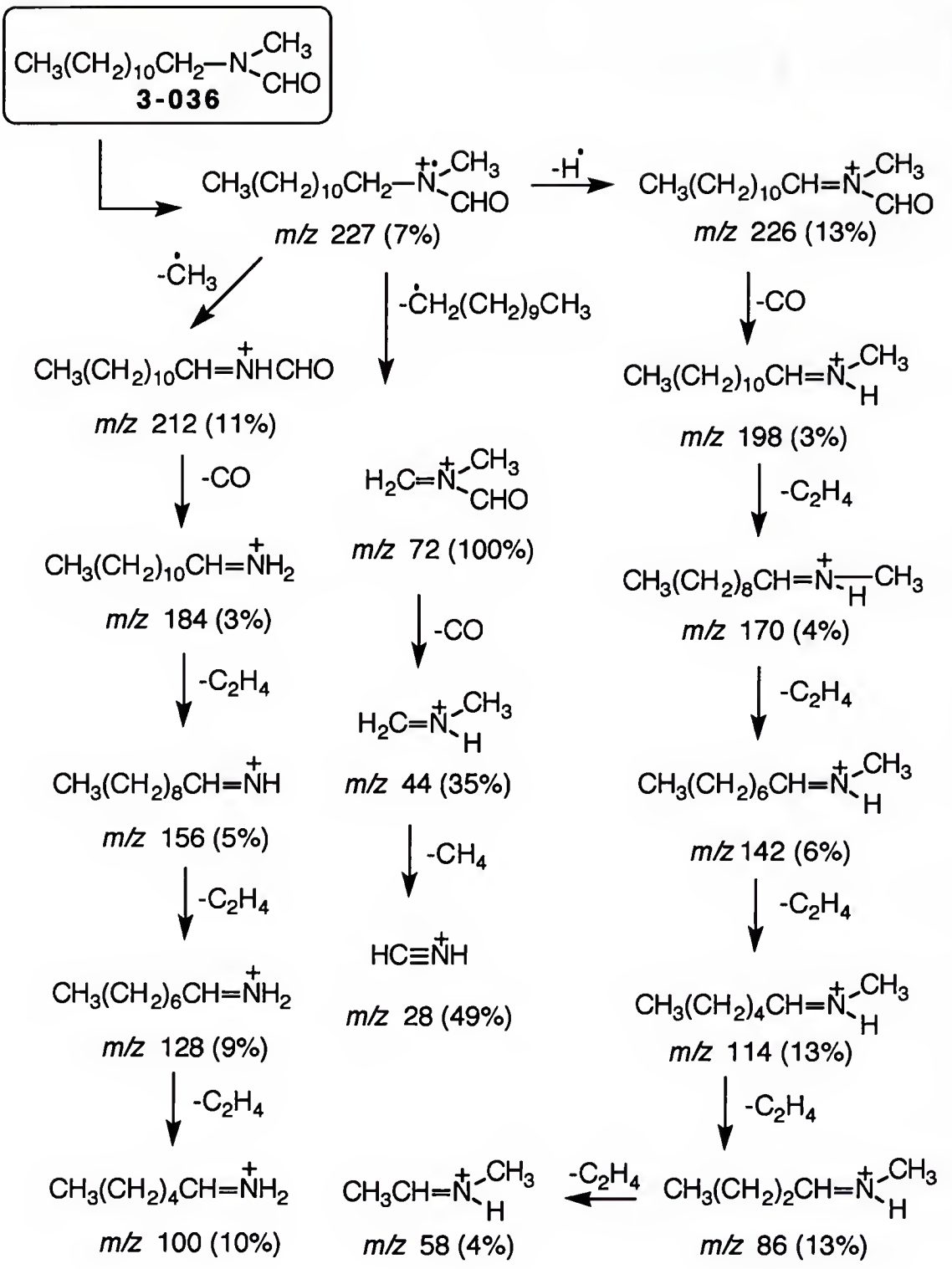
N-Methyl-*N*-1-dodecylformamide (**3-036**) (Scheme B-9) displays its molecular ion at *m/z* 227 (7%). Initial loss of a hydrogen radical generates the ion at *m/z* 226 (13%) from which loss of CO can allow formation of the ion at *m/z* 198 (3%). The ion corresponding to *m/z* 198 can fragment by sequential loss of ethylene molecules to yield the peaks observed at *m/z* 170 (4%), 142 (6%), 114 (13%), 86 (13%) and 58 (4%) respectively.

α-Cleavage to yield the undecyl radical generates the base peak at *m/z* 72 (100%). Loss of CO from the base peak gives the ion at *m/z* 44 (35%), from which the ion at *m/z* 28 (49%) could be explained by loss of methane. Radical cleavage of the *N*-methyl bond generates ion at *m/z* 112 (11%). Sequential loss of CO and ethylene generates the series of ions differing by 28 mass units: 184 (3%), 156 (5%), 128 (9%) and 100 (10%).

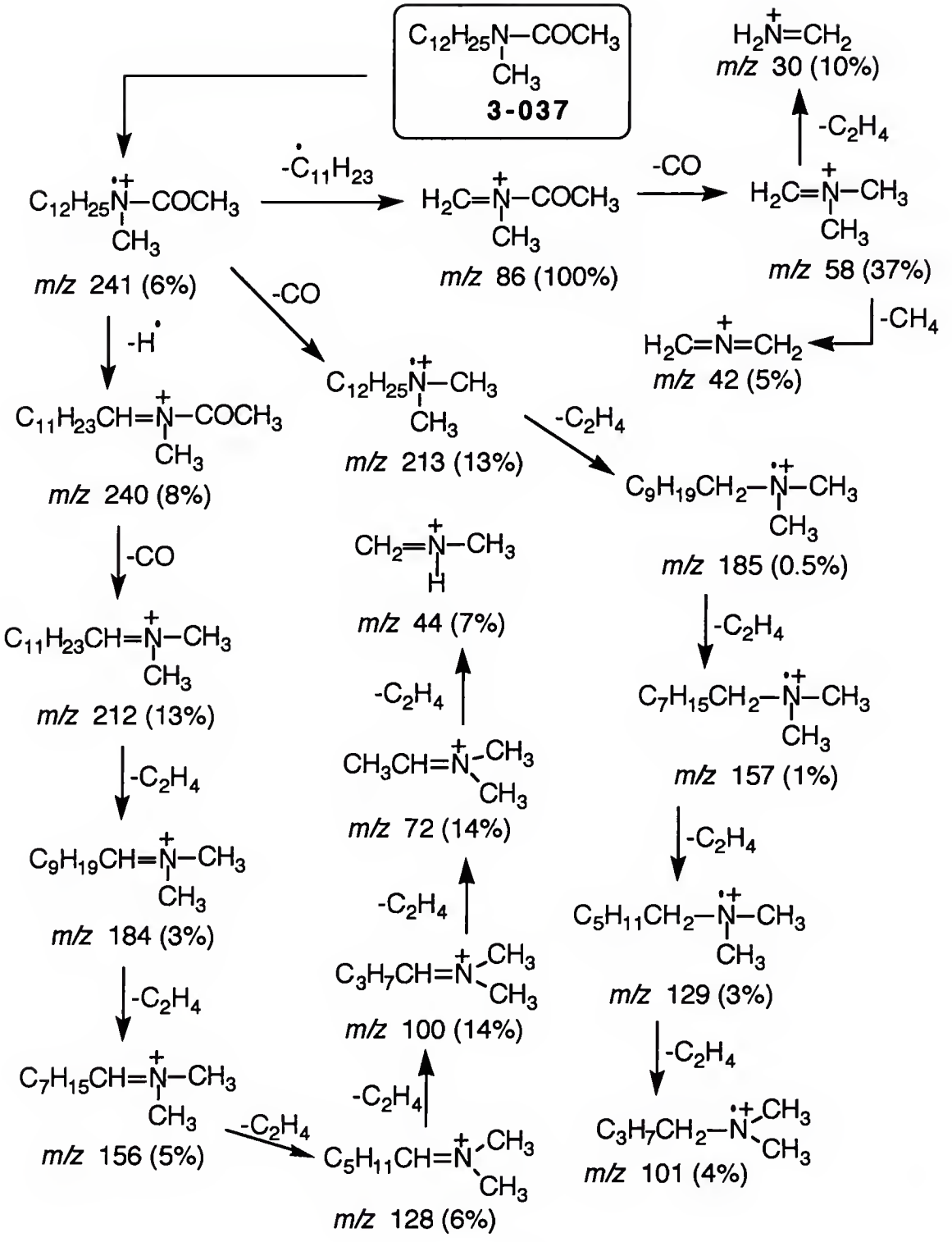
Fragmentation of *N*-methyl-*N*-1-dodecylacetamide (**3-037**) (Scheme B-10)

N-Methyl-*N*-1-dodecylacetamide (**3-037**) (Scheme B-10) displays its molecular ion at *m/z* 241 (6%). α-Cleavage of an undecyl radical generates the base peak at *m/z* 86 (100), which may lose CO to give the ion at *m/z* 58 (37%). From this ion (*m/z* 58) loss of ethylene and methane generates the ions at *m/z* 30 (10%) and *m/z* 42 (5%), respectively.

The molecular ion can lose a hydrogen radical to form the M^+-1 ion at *m/z* 240 (8%), from which loss of CO leads to the ion at *m/z* 212 (13%). Consecutive loss of ethylene molecules generates the following series of ion :- *m/z* 184 (3%), 156 (5%), 128 (6%), 100 (14%), 72 (14%) and 44 (7%). Similarly, loss of CO from the molecular ion leads to the ion at *m/z* 213 (13%), from which loss of multiples of 28 mass units (ethylene molecules) generates the series of ions indicated.


CH3(CH2)10CH2—N(CH3)(CHO)
3-036
CH3(CH2)10CH2—N+•(CH3)(CHO)
m/z 227 (7%)
-H•
CH3(CH2)10CH=N+(CH3)(CHO)
m/z 226 (13%)
-•CH3
-•CH2(CH2)9CH3
-CO
CH3(CH2)10CH=N+HCHO
m/z 212 (11%)
H2C=N+(CH3)(CHO)
m/z 72 (100%)
CH3(CH2)10CH=N+(CH3)H
m/z 198 (3%)
-CO
-C2H4
CH3(CH2)10CH=N+H2
m/z 184 (3%)
H2C=N+(CH3)H
m/z 44 (35%)
CH3(CH2)8CH=N+(H)CH3
m/z 170 (4%)
-C2H4
-CH4
CH3(CH2)8CH=N+H
m/z 156 (5%)
HC≡N+H
m/z 28 (49%)
CH3(CH2)6CH=N+(CH3)H
m/z 142 (6%)
CH3(CH2)6CH=N+H2
m/z 128 (9%)
CH3(CH2)4CH=N+(CH3)H
m/z 114 (13%)
CH3(CH2)4CH=N+H2
m/z 100 (10%)
CH3CH=N+(CH3)H
m/z 58 (4%)
CH3(CH2)2CH=N+(CH3)H
m/z 86 (13%)

Scheme B-9


C12H25N(CH3)–COCH3
3-037
m/z 241 (6%)
-C11H23
H2C=N(CH3)–COCH3
m/z 86 (100%)
-CO
H2C=N(CH3)–CH3
m/z 58 (37%)
-C2H4
H2N=CH2
m/z 30 (10%)
-CH4
H2C=N=CH2
m/z 42 (5%)
-H
C11H23CH=N(CH3)–COCH3
m/z 240 (8%)
-CO
C12H25N(CH3)–CH3
m/z 213 (13%)
-C2H4
C9H19CH2–N(CH3)–CH3
m/z 185 (0.5%)
-C2H4
C7H15CH2–N(CH3)–CH3
m/z 157 (1%)
-C2H4
C5H11CH2–N(CH3)–CH3
m/z 129 (3%)
-C2H4
C3H7CH2–N(CH3)2
m/z 101 (4%)
-CO
C11H23CH=N(CH3)–CH3
m/z 212 (13%)
-C2H4
CH2=N(CH3)–CH3
m/z 44 (7%)
-C2H4
C9H19CH=N(CH3)–CH3
m/z 184 (3%)
-C2H4
CH3CH=N(CH3)2
m/z 72 (14%)
-C2H4
C7H15CH=N(CH3)–CH3
m/z 156 (5%)
-C2H4
C3H7CH=N(CH3)2
m/z 100 (14%)
-C2H4
C5H11CH=N(CH3)2
m/z 128 (6%)

Scheme B-10

Fragmentation of *N*-acetyl-*N*-1-dodecylformamide (**3-038**) (Scheme B-11)

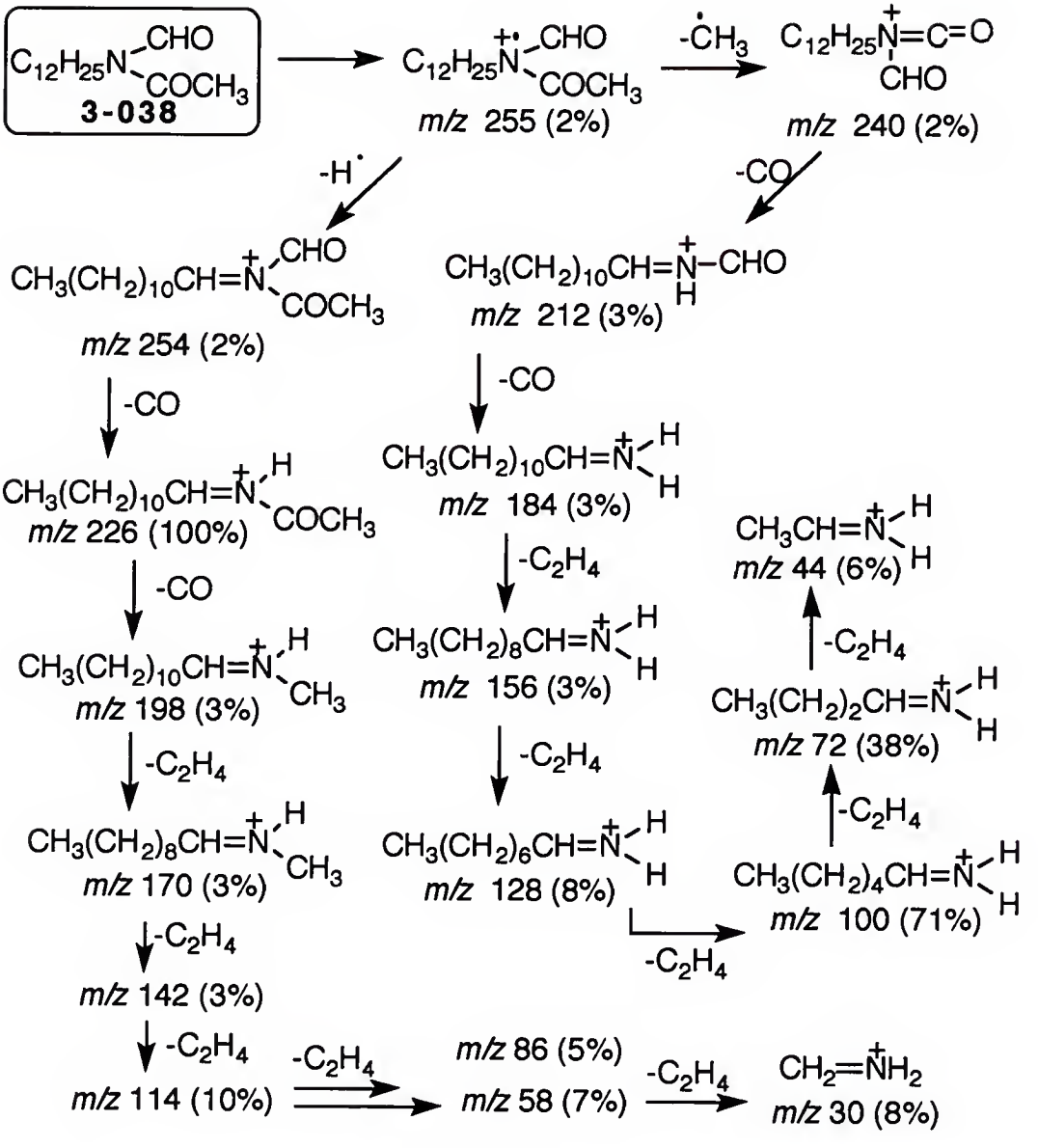
N-Acetyl-*N*-1-dodecylformamide (**3-038**) (Scheme B-11) displays its molecular ion at *m/z* 255 (2%). Two major fragmentation pathways have been noted, firstly loss of a hydrogen radical generates the ion at *m/z* 254 (2%) which can lose CO to yield the base peak at *m/z* 226 (100%). The base peak can fragment by loss of CO to yield the ion at *m/z* 198 (3%) followed by sequential loss of ethylene to generate the ions at *m/z* 170 (3%), 142 (3%), 114 (10%), 86 (5%), 58 (7%) and 30 (8%).

The other likely major fragmentation pathway involves initial loss of a methyl radical from the base peak to yield the ion at *m/z* 240 (2%) followed by sequential loss of two molecules of CO to generate ions at *m/z* 212 (3%) and 184 (3%) respectively. Further fragmentation from *m/z* 184 by sequential loss of ethylene can generate the ions observed at *m/z* 156 (3%), 128 (8%), 100 (71%), 72 (38%), and 44 (6%).

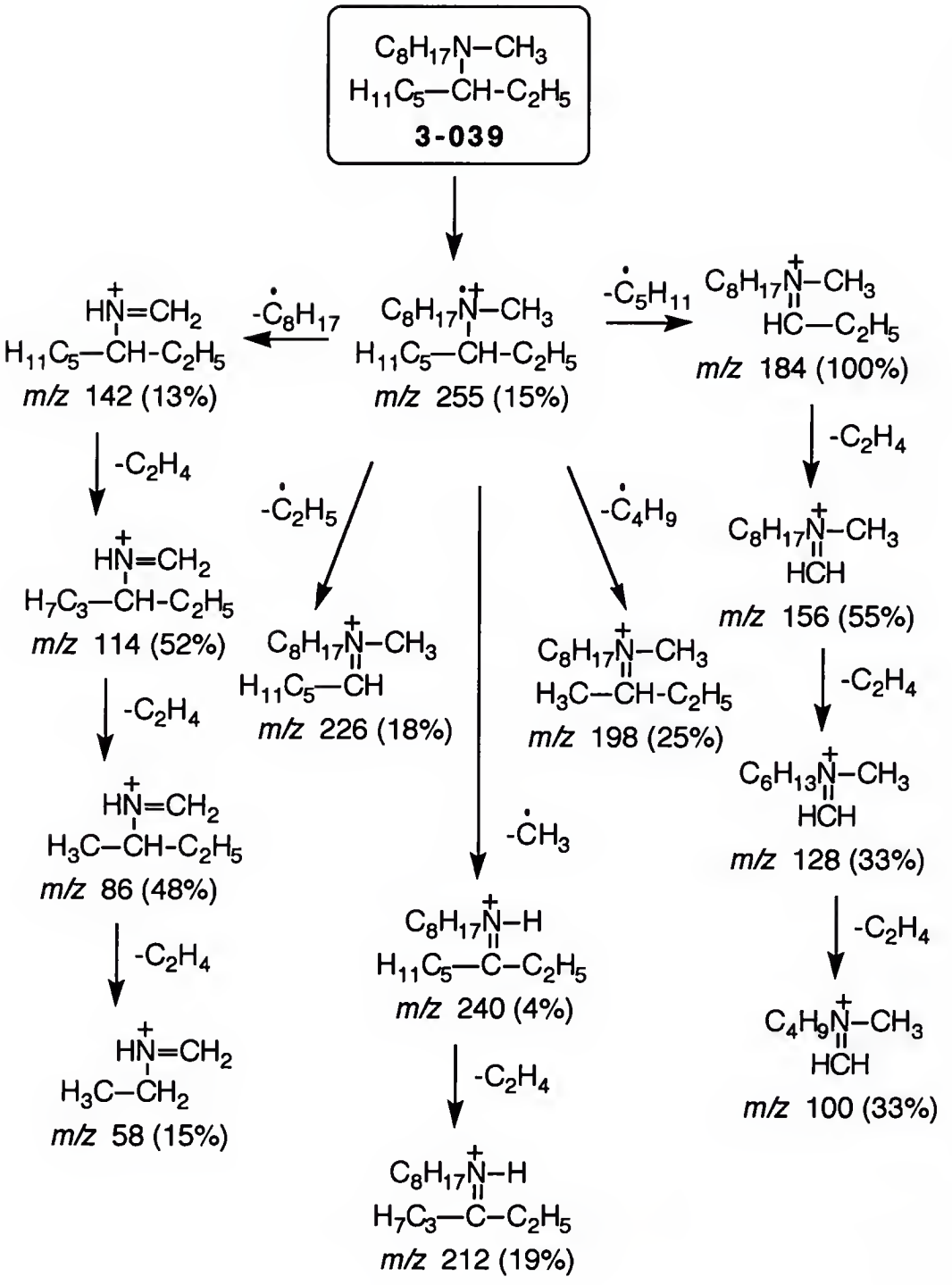
Fragmentation of *N*-methyl-*N*-3-octyl-1-octylamine (**3-039**) (Scheme B-12)

N-Methyl-*N*-3-octyl-*N*-1-octylamine (**3-039**) (Scheme B-12) displays its molecular ion at *m/z* 255 (15%). Radical cleavage constituted most of the pathways for the subsequent ions formed from the molecular ion. α-Cleavage of a pentyl radical led to the base peak at *m/z* 184 (100%).

Cleavage of a methyl radical from the molecular ion generated the ion at *m/z* 240 (4%) which could then lose ethylene to form the ion at *m/z* 212 (19%). Also, cleavage of an octyl radical leads to the ion at *m/z* 142 (13%), while cleavage of a butyl radical led to the ion at *m/z* 198 (25%). Cleavage of an ethyl radical from the molecular ion generates the peak at *m/z* 226 (18%). The ions at *m/z* 142 and *m/z* 184 (the base peak) could undergo further fragmentation through loss of ethylene molecules (multiples of 28 mass units) to generate the ion pathways indicated, as described above for the other (long chain) aliphatic compounds.


3-038
m/z 255 (2%)
m/z 240 (2%)
m/z 254 (2%)
m/z 212 (3%)
m/z 226 (100%)
m/z 184 (3%)
m/z 198 (3%)
m/z 156 (3%)
m/z 170 (3%)
m/z 128 (8%)
m/z 142 (3%)
m/z 100 (71%)
m/z 114 (10%)
m/z 86 (5%)
m/z 58 (7%)
m/z 44 (6%)
m/z 72 (38%)
m/z 30 (8%)

Scheme B-11

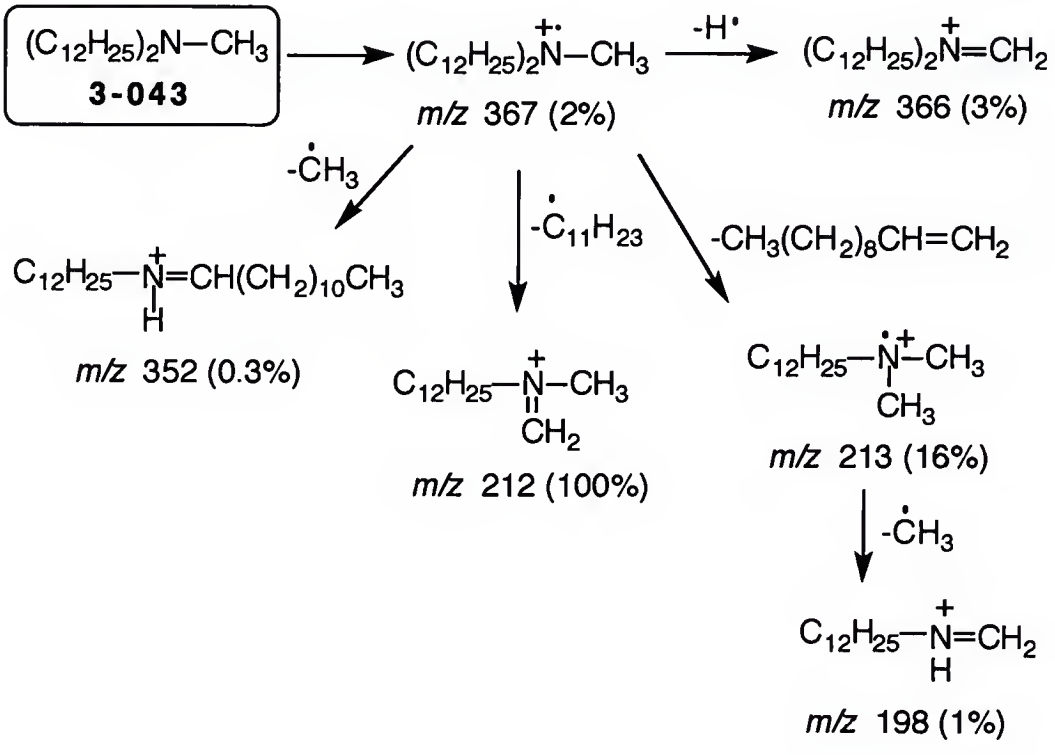

C8H17N–CH3
H11C5–CH-C2H5
3-039
m/z 255 (15%)
-C8H17
HN=CH2
H11C5–CH-C2H5
m/z 142 (13%)
-C2H4
HN=CH2
H7C3–CH-C2H5
m/z 114 (52%)
-C2H4
HN=CH2
H3C–CH-C2H5
m/z 86 (48%)
-C2H4
HN=CH2
H3C–CH2
m/z 58 (15%)
-C5H11
C8H17N–CH3
HC–C2H5
m/z 184 (100%)
-C2H4
C8H17N–CH3
HCH
m/z 156 (55%)
-C2H4
C6H13N–CH3
HCH
m/z 128 (33%)
-C2H4
C4H9N–CH3
HCH
m/z 100 (33%)
-C2H5
C8H17N–CH3
H11C5–CH
m/z 226 (18%)
-C4H9
C8H17N–CH3
H3C–CH-C2H5
m/z 198 (25%)
-CH3
C8H17N–H
H11C5–C–C2H5
m/z 240 (4%)
-C2H4
C8H17N–H
H7C3–C–C2H5
m/z 212 (19%)

Scheme B-12

Fragmentation of *N*-methyldi-1-dodecylamine (**3-043**) (Scheme B-13)

N-Methyldi-1-dodecylamine (**3-043**) (Scheme B-13) displays its molecular ion at *m/z* 367 (2%). Loss of an undecyl radical generates the base peak at *m/z* 212 (100%).

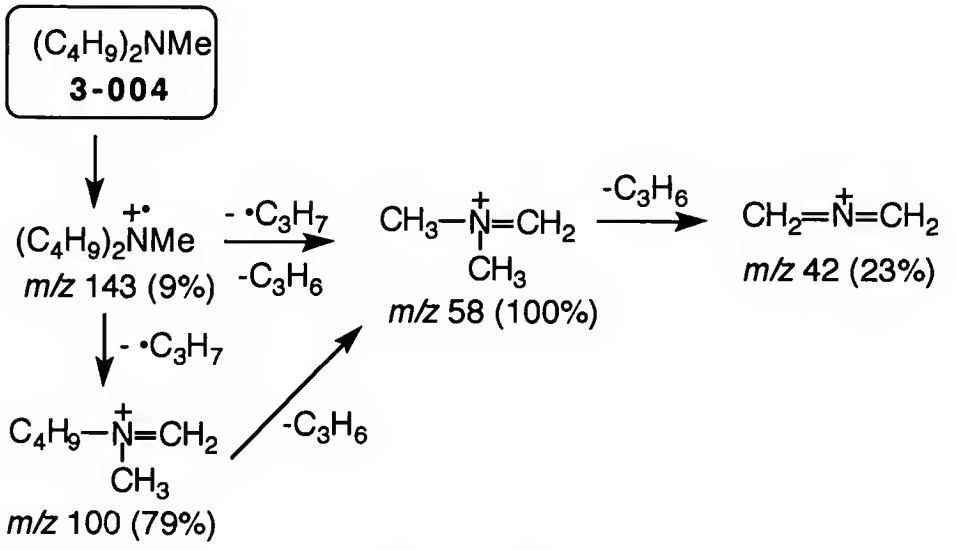
Three other possible fragmentation pathways have been noted. Firstly, the molecular ion can lose an undecene molecule to yield the ion at *m/z* 213 (16%) which can further lose a methyl radical to generate the ion at *m/z* 198 (1%). Secondly, a methyl radical can be lost with subsequent hydrogen rearrangement to yield the ion of very weak intensity at *m/z* 352 (0.3%). In addition, the molecular ion can lose a hydrogen radical to generate the ion at *m/z* 366 (3%).



Scheme B-13

Fragmentation of *N*-methyldi-1-butylamine (**3-004**) (Scheme B-14)

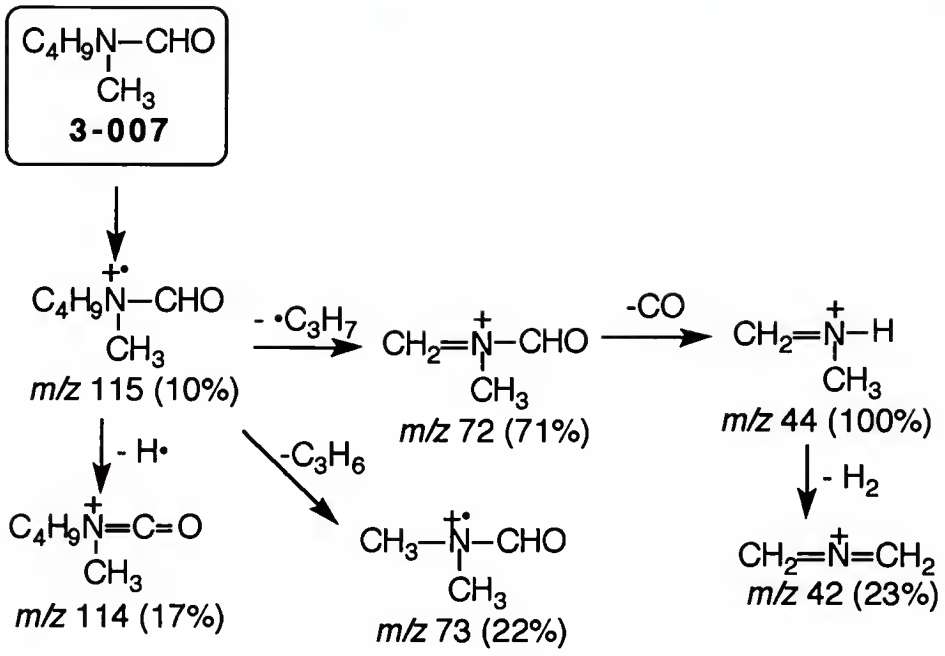
N-Methyldi-1-butylamine (**3-004**) (Scheme B-14) displays its molecular ion at *m/z* 143 (9%). The base peak (*m/z* 58) may be formed *via* two possible pathways: (i) loss of a propyl radical coupled with loss of propene or (ii) loss of a propyl radical to generate the ion at *m/z* 100 (79%) which would eventually lose propene. Loss of methane from the base peak would lead to the ion at *m/z* 42 (23).



Scheme B-14

Fragmentation of *N*-methyl-*N*-1-butylformamide (**3-007**) (Scheme B-15)

N-Methyl-*N*-1-butylformamide (**3-007**) (Scheme B-15) displays its molecular ion at *m/z* 115 (10%). Loss of a propyl radical leads to the formamide ion at *m/z* 72 (71%). Further loss of CO from this ion gives the base peak at *m/z* 44. The molecular ion underwent loss of propene to generate the ion at *m/z* 73 (22%) and loss of a hydrogen radical to generate the ion at *m/z* 114 (17%).



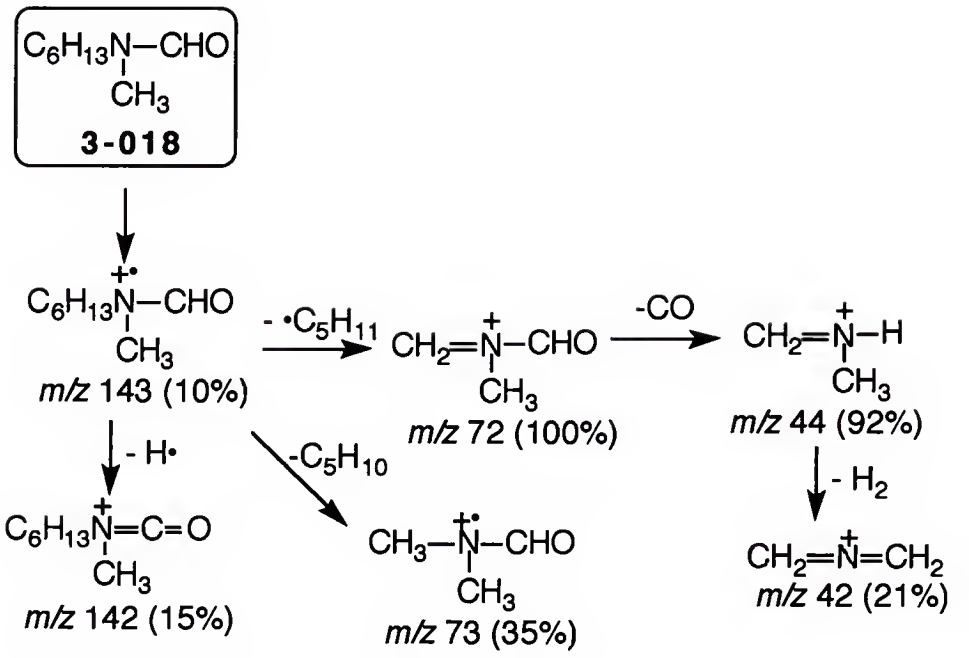
Scheme B-15

Fragmentation of *N*-methyl-*N*-1-hexylformamide (**3-018**) (Scheme B-16)

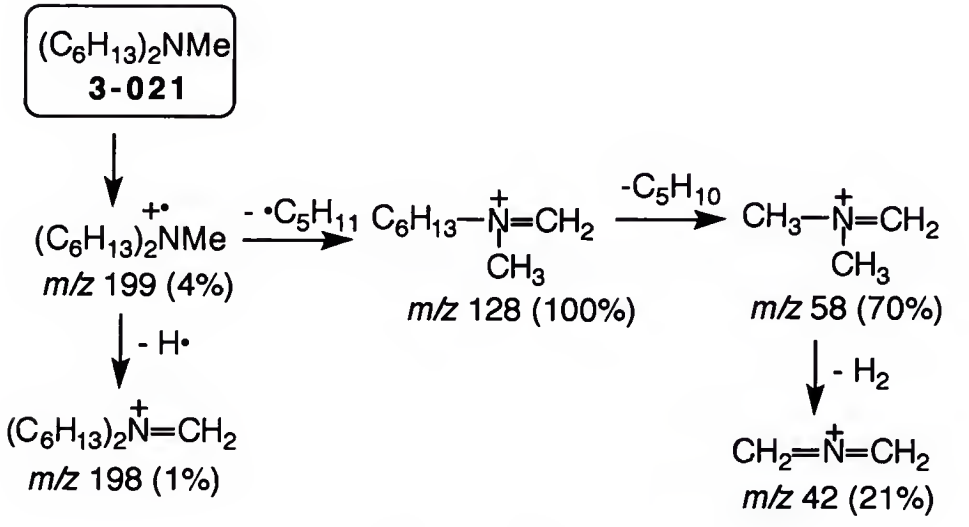
N-Methyl-*N*-1-hexylformamide (**3-018**) (Scheme B-16) displays its molecular ion at *m/z* 115 (10%). Loss of a propyl radical the base peak at *m/z* 72 (100%). Further loss of CO from the base peaks gives the ion at *m/z* 44 (92%). The ion at *m/z* 44 could also lose molecular hydrogen to generate the ion at m/z *42* (21%). The molecular ion underwent loss of pentene to generate the ion at *m/z* 73 (22%). Loss of a hydrogen radical from the molecular ion generated the M^+-H ion at *m/z* 142 (15%).

Fragmentation of *N*-methyldi-1-hexylamine (**3-021**) (Scheme B-17)

N-Methyldi-1-hexylamine (**3-021**) (Scheme B-17) displays its molecular ion at *m/z* 143 (4%). Loss of a pentyl radical provided the base peak at *m/z* 128. The base peak could then lose pentene to form the ion at *m/z* 58 (70%), which through loss of molecular hydrogen could lead to the ion at *m/z* 42 (21%). The M^+-H (*m/z* 198) was observed with a low intensity (1%).



Scheme B-16



Scheme B-17

APPENDIX C
X-RAY CRYSTAL STRUCTURE OF BENZOTRIAZOLE-1-CARBOXAMIDINIUMTOSYLATE

The structure of benzotriazole-1-carboxamidinium tosylate (**4-013**) was further verified by single crystal X-ray crystallography, which was performed by Peter J. Steel.[C.1] Figure C-1 shows a perspective view and atom labelling of the X-ray structure of **4-013**. The NH hydrogen atoms were located from a difference map and this confirms that in the solid state this compound exists as the carboxamidinium tosylate salt. The bonding geometry is comparable to that found in structurally related compounds. The carboxamidinium group is twisted slightly out of the plane of the benzotriazole ring system (angle between mean planes = 20.4°). An interesting feature of the structure is the molecular packing which is controlled by a complex network of intermolecular hydrogen bonds. In particular, each of the four NH hydrogen atoms is hydrogen bonded to an oxygen atom of an adjacent tosylate anion, with one of these oxygens (O1) forming a bridge to two NH hydrogens (H11A and H12B) of adjacent cations. The N - O distances lie in the range 2.76 - 2.85 Å. As a result, the molecules pack in chains along the *a* axis which creates channels of hydrophilic and hydrophobic regions that alternate along the *c* axis of the unit cell.

C.1 Peter J. Steel, Department of Chemistry, University of Canterbury, Christchurch 1, New Zealand.

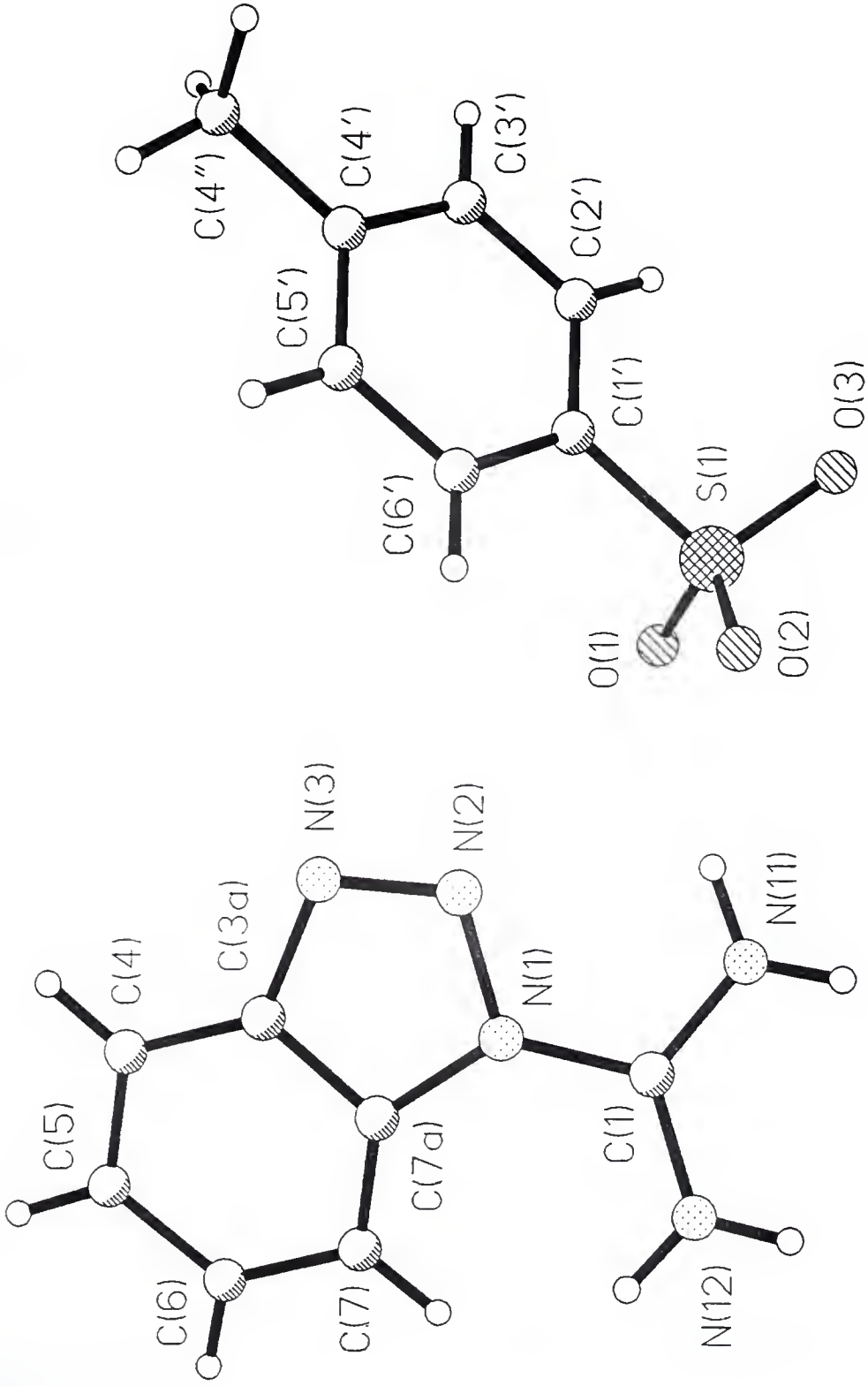


Figure C-1 Perspective view of the crystal structure of benzotriazole-1-carboxamidinium tosylate (4-013)

X-ray crystal structure of (**4-013**)[C.2]

Crystal data. $C_{14}H_{15}N_5O_3S$, colorless plate, 0.38 x 0.36 x 0.02 mm; orthorhombic, Pbca; a = 12.504(4), b = 9.471(3), c = 25.929(7) Å, V = 3071(2) Å^3; T = -143 °C, D_c = 1.42 g cm^{-3}; Z = 8, F(000) = 1392.

Data collection, structure solution and refinement. All measurements were made with a Nicolet P4s diffractometer using graphite monochromatized Mo Kα (λ = 0.71073Å) radiation. Throughout the data collection (ω scans, $2\theta_{max} = 46°$) the intensities of the three standard reflections were monitored at regular intervals and no significant crystal decomposition was indicated. Intensities were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods using SHELXS-90 [90AX467], and refined on F^2 by full matrix least-squares procedures using SHELXL-92. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.3 times the isotropic equivalent of their carrier atoms. The function minimized was $\Sigma w (F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2)]^{-1}$. The 209 parameters were refined to $wR^2 = 0.1040$ for all 2130 unique measured reflections. The final conventional *R* value was 0.049 for 607 reflections with $F_o > 4\sigma(F_o)$. Final difference map features were all < 0.27 e Å^{-3}. Final non-hydrogen atom coordinates are given in Table C-1. Full tables of atom coordinates, thermal parameters, bond lengths, bond angles and structure factors have been deposited with the Cambridge Crystallographic Data Base.

C.2 Data obtained by Dr. Peter J. Steel for a crystal submitted by the writer.

Table C-1. Atom coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **4-013**

Atom	x	y	z	U_{eq}
N(1)	2352(5)	468(7)	3421(2)	23(2)
N(2)	3130(5)	1025(7)	3750(2)	26(2)
N(3)	2694(4)	1914(7)	4046(2)	21(2)
C(3A)	1575(6)	1990(9)	3926(3)	22(2)
C(4)	800(5)	2841(8)	4137(3)	26(2)
C(5)	-196(6)	2716(9)	3934(3)	26(2)
C(6)	-404(5)	1786(8)	3517(3)	24(2)
C(7)	370(5)	956(7)	3304(3)	16(2)
C(7A)	1354(5)	1069(8)	3524(3)	16(2)
C(1)	2684(6)	-512(8)	3052(3)	18(2)
N(11)	3703(4)	-559(6)	2944(2)	20(2)
N(12)	1975(4)	-1345(5)	2834(2)	24(2)
C(1')	6288(5)	3001(8)	3670(2)	16(2)
C(2')	7136(5)	3940(7)	3658(3)	21(2)
C(3')	7337(5)	4761(7)	4092(3)	19(2)
C(4')	6713(6)	4668(8)	4529(3)	26(2)
C(5')	5857(6)	3726(8)	4520(3)	26(2)
C(6')	5642(5)	2876(9)	4101(3)	22(2)
S(1)	6007(1)	1978(2)	3120(1)	21(1)
O(1)	5212(3)	2799(5)	2812(2)	18(1)
O(2)	5577(3)	626(5)	3302(2)	18(1)
O(3)	7021(3)	1832(5)	2839(2)	17(1)
C(4")	6953(6)	5583(8)	4999(3)	51(3)

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The reference citation system employed throughout this dissertation is that from "*Comprehensive Heterocyclic Chemistry* " (vol. I), Pergamon Press, Oxford, 1984. The series is edited by Alan R. Katritzky, FRS and Charles R. Rees, FRS. Each time a reference is cited a number and letter code appears in brackets, for example [00ABC000]. The first two digits denote the year in units of ten (four digits appear for years not from the 20th century), the letter code is an abbreviation for the journal or book cited and the last digit(s) represent(s) the page number.

Additional notes to the system are as follows:

(i) The references are listed consecutively by year, alphabetical by the journal code and then by page number.

(ii) Each reference code is followed by the conventional literature citation complete with the names of the authors.

(iii) Journals which are published in more than one part, or more that one volume per year are cited with the appropriate part or volume.

(iv) Patents are cited with appropriated three letter codes to denote country of origin.

(v) Books which are frequently cited are preceded by the letter B.

(vi) Books and journals which are less commonly used coded 'MI' for miscellaneous.

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BIOGRAPHICAL SKETCH

Roslyn L. (Parris) White was born in June, 1967, on the island of Barbados, West Indies, the seventh of nine children. She emigrated to Boston, Massachusetts in 1984 and completed high school. She then went on to receive her B.A.*cum laude* in chemistry from Regis College in Weston, Massachusetts, in 1990.

She commenced the Ph.D. program in the Chemistry Department of the University of Florida in August of 1990 under the supervision of Dr. J. Eric Enholm. In December, 1992, she switched research groups and continued the program under the supervision of Dr. Alan R. Katritzky.

She was married in August, 1994 to her college sweetheart, Abdul White, in the city of Boston, Massachusetts.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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May, 1995

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